EDITORIAL
253 Retinol and Retinol-Binding Protein in Cerebrospinal Fluid: Can Vitamin A Take the "Idiopathic" Out of Idiopathic Intracranial Hypertension?  
Jenny Libien and William S. Blaner

ORIGINAL CONTRIBUTIONS
258 Retinol-Binding Protein and Retinol Analysis in Cerebrospinal Fluid and Serum of Patients With and Without Idiopathic Intracranial Hypertension  

263 The Prevalence of Relative Afferent Pupillary Defects in Normal Subjects  
Helmut Wilhelm, Tobias Peters, Holger Lüdtke, and Barbara Wilhelm

268 Spatial Processing in Bálint Syndrome and Prosopagnosia: A Study of Three Patients  
Jason J. S. Barton, George L. Malcolm, and Rebecca L. Hefter

275 Closely Spaced Stressful Life Events Precede the Onset of Benign Essential Blepharospasm and Hemifacial Spasm  
Lenworth N. Johnson, Ryan W. Lapour, Gabriella M. Johnson, Patricia J. Johnson, Richard W. Madsen, and Steven A. Hackley

281 Endovascular Treatment of a Bilateral Ophthalmic-Ethmoidal Artery Dural Arteriovenous Fistula  
Vassilios Katsaris, Chrysanthi Papagiannaki, and Constantinos Violis

285 Posterior Ischemic Optic Neuropathy After Minimally Invasive Prostatectomy  
Eric D. Weber, Marcus H. Colyer, Robert L. Lesser, and Prem S. Subramanian

288 Bilateral Macular Retinitis as the Presenting Feature of Subacute Sclerosing Panencephalitis  
Rajesh B. Babu and Jyotirmay Biswas

292 Isolated Cortical Visual Loss With Subtle Brain MRI Abnormalities in a Case of Hypoxic-ischemic Encephalopathy  
Edward Margolin, Sachin K. Gujar, and Jonathan D. Trobe

297 Room Tilt Illusion Influenced by Head Position  
Chen Zhao, Shasha Lu, Nadja Tajouri, Konstantinos Afferis, Theodor Landis and Avinoam B. Saffran

300 Migraine-like Visual Hallucinations as the Presenting Manifestations of Focal Seizures in Neurocysticercosis  
Sanjeev Jha and Rajesh Kumar

304 Exotropia and Face Turn in Children With Homonymous Hemianopia  
Sean P. Donahue and Alden K. Haun

(continued on next page)
Contents (continued)

308 Reversible Tonic Pupils
Caroline A. A. Hulsman and Christine T. Langerhorst

LETTERS TO THE EDITOR
310 Tonic Pupil as the Presenting Sign of Relapsed Acute Myeloid Leukemia
Mandagere R. Vishwanath and Stephen J. Charles
311 Generalized Myasthenia Gravis Triggered by Cataract Surgery
Soma Sahai-Srivastava and Tina C. Lin
312 Benztropine-induced Esotropia and Mydriasis
Sun-Young Oh, Byoung-Soo Shin, Yeon-Hee Lee, Ae Young Lee, and Ji Soo Kim
313 Idiopathic Intracranial Hypertension in a Transgender Man
Clinton Sheets, Marc Peden, and John Guy
315 Simultaneous Ischemic Optic Neuropathy and Third Cranial Nerve Palsy in Giant Cell Arteritis
Çağatay Oncel, Ferda Bir, and L. Sinan Bir

NEURO-OPHTHALMOLOGY AT LARGE
317 Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO)
Fort Lauderdale, Florida, May 6–10, 2007
Swaraj Bose and Howard D. Pomeranz
321 The 59th Annual Meeting of the American Academy of Neurology, Boston, Massachusetts
April 28–May 5, 2007
Tracy Wang and Mark L. Moster

BOOK REVIEWS
330 Optic Nerve Disorders, 2nd Edition
Jonathan D. Trobe
330 How to Examine the Nervous System, 4th Edition
Gregory P. Van Stavern
331 Human Brain Anatomy in Computerized Images, 2nd Edition
Julie A. Matsumoto
332 Thieme Atlas of Anatomy: Head and Neuroanatomy
Jonathan D. Trobe
332 Medical Decision Making
Steven A. Newman
333 Ophthalmic Ultrasound: A Diagnostic Atlas, 2nd Edition
Jonathan J. Dutton
333 Clinical and Basic Oculomotor Research
Louis F. Dell’Osso
334 Fundamentals of Neurology: An Illustrated Guide
Jonathan D. Trobe
334 Ultimate Review for the Neurology Boards
Russell H. Swerdlow

CALENDAR
336

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ERRATUM
Due to an editing error, spelling errors appeared in the author listing of the article “Efficacy of Corticosteroids and and External Beam Radiation in the Management of Moderate to Severe Thyroid Eye Disease” in the September 2007 issue (J Neuro-ophthalmol 2007;27:205–14). The following text should have appeared at the end of the author listing: for the Neuro-Ophthalmology Research and Development Consortium (NORDIC) Thyroid Eye Disease (TED) Study Committee. We regret any inconvenience this may have caused.

Instructions for Authors appear in the March issue or online at www.jneuro-ophthalmology.com

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Retinol and Retinol-Binding Protein in Cerebrospinal Fluid: Can Vitamin A Take the ‘‘Idiopathic’’ Out of Idiopathic Intracranial Hypertension?

Jenny Libien, MD, PhD and William S. Blaner, PhD

Idiopathic intracranial hypertension (IIH), by definition of unknown etiology, may be in need of a new name. The article by Warner et al in this issue of the *Journal of Neuro-Ophthalmology* (1) offers evidence that abnormal retinol (vitamin A) transport and metabolism is involved in the pathogenesis of the disease. There is a significant elevation of the retinol to retinol-binding protein (RBP) ratio with less RBP and more unbound retinol in the cerebrospinal fluid (CSF) of patients with IIH than of control subjects. To grossly simplify and to extrapolate, the findings suggest that IIH results from vitamin A toxicity localized to the CSF.

Vitamin A toxicity has long been acknowledged as a cause of the severe headaches and papilledema associated with intracranial hypertension. The classic tale is of the Eskimo (Inuit) who for centuries have hunted polar bears for fur and meat but do not eat the liver for fear of the headaches and blurred vision that result from ingestion. Polar bears, as carnivores at the top of the Arctic food chain, have very high hepatic vitamin A levels. Human consumption of their livers would induce acute vitamin A toxicity. Although polar bear liver is not part of our modern day diet, chronic excessive consumption of foods rich in vitamin A has been linked to intracranial hypertension. Case reports of a “carrot craver” (2) and several “liver lovers” (3) (of cow—not polar bear—liver) describe elevated intracranial pressure with complete resolution after removal of the offending foods from the diet. Intracranial hypertension and/or papilledema associated with hypervitaminosis A has also been reported in a number of “vitamin junkies” (added to the lexicon in the spirit of carrot cravers and liver lovers) and in children and teenagers given vitamin A for treatment of acne and other ailments in decades past. The doses leading to elevated intracranial pressure have ranged from 25,000 to 200,000 IU of vitamin A per day and were taken for months to years before diagnosis (4,5). (The recommended daily allowance of vitamin A is 2,300–3,000 IU).

Intracranial hypertension is also a well-documented side effect of therapeutic doses of the synthetic vitamin A derivative 13-cis-retinoic acid (generic name isotretinoin; brand name Accutane) (6) used for treatment of acne and of the vitamin A metabolite all-trans-retinoic acid used in the treatment of acute promyelocytic leukemia (7,8). In an analysis of adverse ocular events after 13-cis-retinoic acid treatment that were reported to the Food and Drug Administration, the World Health Organization Spontaneous Reporting System, and the National Registry of Drug-Induced Ocular Side Effects at the Casey Eye Institute, Fraunfelder et al (9) identified 179 cases of intracranial hypertension associated with 13-cis-retinoic acid, with 6 of the cases having a positive rechallenge, a mean time of 2.3 months between initial exposure and diagnosis, and documented resolution of 86 cases within weeks to a few months after cessation of the drug.
The hypothesis that abnormal vitamin A metabolism is a cause of IIH in patients with normal vitamin A consumption has been previously investigated and the published findings are summarized in Table 1. In the first reported clinical study, Jacobson et al (10) measured serum retinol concentrations from 16 women with IIH and 70 control women. The investigators reported a median serum retinol concentration of 75.2 μg/dL in the IIH group compared with 53.0 μg/dL in the control group. Although the median serum retinol level was higher in patients with IIH than in the control subjects, there was considerable overlap between the two groups with only two of patients with IIH having serum retinol concentrations above the highest control value. Warner et al (1) similarly found high serum retinol levels in patients with IIH compared with anesthesia control subjects. Other researchers have found no significant difference in serum retinol concentrations between patients with IIH and control subjects (11,12) but have identified different indicators of abnormal retinol transport and metabolism in IIH. In a previous publication from Warner et al (13), retinol levels were higher in the CSF in patients with IIH than in patients with normal intracranial pressure but were not elevated in patients with intracranial hypertension due to venous outflow obstruction, tetracycline use, or systemic disease. Tabassi et al (12) also found higher CSF retinol levels in patients with IIH than in control subjects.

The association of IIH with RBP, the transport protein for retinol, was first reported by Selhorst et al (11), who found high serum RBP in 7 of 30 patients with IIH but in none of the control subjects. The results published by Warner et al in this issue (1) also showed high serum RBP in patients with IIH compared with control subjects when controlling for body mass index (BMI). Their novel finding of low CSF RBP levels and a higher retinol/RBP ratio in CSF will hopefully be replicated by other investigators and will lead to greater understanding of the link between vitamin A and IIH.

The mechanisms by which vitamin A and its synthetic derivatives lead to a reversible elevation in intracranial pressure are not known. Vitamin A is involved in numerous physiologic processes, including vision, cellular differentiation, and embryonic development. The function of vitamin A in the adult brain is only beginning to be understood, but there is evidence for involvement in synaptic plasticity (14,15), memory formation (16,17), cortical synchrony during sleep (18–20), and adult neurogenesis (21–23). Vitamin A acts primarily via its metabolites, which are called retinoids. 11-cis-retinal is the visual chromophore. Outside of the visual system, the major biologically active derivative is all-trans-retinoic acid.

Formation of all-trans-retinoic acid depends on highly regulated processes of retinoid absorption from the diet, transport, and metabolism (24). A model of vitamin A transport and metabolism is given in Figure 1. All retinoids are derived from the diet, with most dietary retinoid in the form of retinyl ester and a minority as retinol and beta-carotene. Retinyl esters are hydrolyzed to retinol within the intestinal lumen by pancreatic triglyceride lipase (25) or by phospholipase B at the intestinal brush border. Retinol is then absorbed from the intestinal lumen into enterocytes and re-esterified by lecithin:retinol acyl transferase (LRAT). The newly formed retinyl esters are incorporated into chylomicrons and secreted by the enterocyte into the lymphatic system and then into the circulation. A minority of the absorbed retinyl esters are delivered to target tissues directly by chylomicrons. However, retinyl ester transport by chylomicrons is an unlikely mechanism of vitamin A delivery involved in the pathogenesis of IIH, as no retinyl esters have been detected in the brain or CSF (26). Most retinyl esters are delivered to the liver where they are hydrolyzed to retinol within hepatocytes. Retinol is then either secreted back into the circulation as retinol bound to RBP or re-esterified by LRAT and stored as retinyl ester in hepatic stellate cells (27). The retinol-RBP complex is then bound by the tetrameric form of transthyretin (TTR) soon after secretion into the circulation.

Retinoid delivery to target tissues occurs predominantly via the retinol-RBP-TTR complex. The liver synthesizes most of the RBP and TTR in the circulation, although adipose tissue also secretes a small percentage of serum RBP. Stra6, an RBP receptor, has recently been identified as a potential facilitator of retinol uptake into some tissues, including brain (28,29). It has been shown to be expressed in the choroid plexus (30). After retinol uptake into the cell, retinol may be oxidized by one of the approximately 15 identified retinol dehydrogenases (RDHs) and then by one of the three known retinaldehyde dehydrogenases (RALDH1–3) to form retinoic acid. In the nucleus, retinoic acid can bind to one of three retinoic acid receptors (RARα,β,γ) and to one of three retinoic acid X receptors (RXRα,β,γ). The RARs and RXRs are members of the steroid/thyroid/retinoid superfamily of ligand-dependent transcription factors that regulate gene transcription via retinoic acid response elements (RAREs) present in approximately 500 genes (31). The concentration of retinoic acid within tissues is generally very low, being usually 100 to 1000 times less than that of retinol (32).

Retinoid transport from the circulation to the CSF and brain is not well characterized. RBP and TTR are synthesized by choroid plexus in levels exceeding hepatic synthesis as a percentage of total protein. TTR comprises approximately 5–25% and RBP 0.5–2.5% of total CSF protein. Choroid plexus-derived RBP and TTR are presumably responsible for retinol transport into CSF. However, it is also possible that TTR does not bind the...
FIG. 1. Simplified scheme for the metabolism and transport of vitamin A in the intestine, liver, brain, and choroid plexus epithelium. Vitamin A is derived from the diet and absorbed across the intestinal mucosa as retinyl ester. Retinyl esters are then packaged into chylomicrons with other lipids and enter the circulation. Chylomicron remnants are taken up by the liver, and the retinyl ester is hydrolyzed to retinol within the hepatocyte. The retinol may then be re-esterified by lecithin:retinol acyl transferase (LRAT) and stored in lipid droplets within hepatic stellate cells or secreted bound to retinol-binding protein (RBP). In the circulation, transthyretin binds the retinol-RBP complex. Retinol is then delivered to tissues throughout the body. Delivery of retinol to brain is thought to involve transport across the vasculature of the choroid plexus into the CSF. RBP secreted by the choroid plexus into the CSF binds retinol and may deliver retinol back to the choroid plexus or to the meninges. Within cells, retinol is hydrolyzed by retinol dehydrogenase (RDH) and then by retinyl aldehyde dehydrogenase (RALDH) to retinoic acid. Retinoic acid binds to its nuclear receptors, retinoic acid receptor (RAR), and retinoid X receptor (RXR), which bind to a retinoic acid receptor element (RARE) and influence gene transcription of one of the approximately 500 retinoic acid-responsive genes.

Retinol-RBP complex in CSF, as the primary role of TTR in serum retinol transport is to add bulk to prevent renal filtration (25). CSF retinol (free, bound to RBP, or bound to RBP-TTR) is most likely delivered to meninges and choroid plexus, both of which express RALDH and have been described as the primary sites of retinoic acid synthesis in postnatal brain (33,34). Interestingly, these primary sites of retinoic acid synthesis are also locations that influence intracranial pressure.

Vitamin A could theoretically lead to intracranial hypertension via enhanced transcription of genes involved in CSF secretion by the choroid plexus or in CSF absorption by arachnoid villi. Aquaporins were proposed as candidate genes linking vitamin A to IIH by Fishman (35) in a commentary on a previous article by Warner et al (13). Aquaporins are membrane water channels that facilitate the transport of water and some small solutes across the membrane (36). Aquaporin 1 is expressed on choroid plexus epithelial cells. Studies of knockout mice show that it influences CSF production and intracranial pressure (37). There is evidence that retinoic acid induces expression of aquaporin-1 in human erythroleukemia HEL cells (38) and of aquaporin-5 in mouse lung epithelial cells (39).

It is possible that altered aquaporin expression is a common pathway in the pathogenesis of IIH and in intracranial hypertension secondary to medications and systemic diseases. Steroid hormones and thyroid hormone, which have also been associated with intracranial hypertension, bind nuclear receptors and influence gene expression in a manner similar to that of retinoic acid.
Minocycline and other tetracycline derivatives, which are also linked to intracranial hypertension, have been shown to block poly(ADP-ribose) polymerase family, member 1 (PARP-1) (40), which also plays a role in gene transcription (41). Further studies are needed to determine whether retinoic acid, steroid and thyroid hormones, and drugs such as minocycline can alter aquaporin expression in choroid plexus, arachnoid villi, or ependymal cells and thereby increase intracranial pressure.

An alternative but intriguing explanation for the association of IIH with abnormal vitamin A transport and metabolism centers on the recent recognition that RBP may act as a signaling molecule (42-44). Adipose tissue-derived RBP, referred to as RBP4 in the diabetes and obesity literature, has been shown to act as an adipokine and modulate insulin sensitivity (43). It is more highly expressed in visceral than in subcutaneous fat and is a marker of intra-abdominal fat mass (45). The increase in serum RBP in some patients with IIH reported by Selhorst et al (11) and the higher serum RBP when controlling for BMI reported by Warner et al in this issue (1) is, therefore, of considerable interest. Could adipose tissue-derived RBP be the missing link between obesity and IIH? Obesity is present in 90% of women, 60% of men, and 30% of children with IIH (46). Furthermore, IIH resolves more rapidly in patients with significant weight loss (47). These findings are consistent with the idea that a signal from adipose tissue (such as RBP) might somehow be involved in triggering elevated intracranial pressure. Because most serum RBP is secreted by the liver and only approximately 15-20% is from adipose tissue, it is possible that a small increase in RBP from adipose tissue would be difficult to detect. This phenomenon may account for why serum RBP was elevated in only some of the patients with IIH in the study by Selhorst et al (11). Warner et al (1) also described low levels of RBP in CSF. One could imagine that choroid plexus-derived RBP also acts as a signaling molecule and alters CSF secretion or absorption.

The major argument against the idea that RBP in serum or CSF directly affects intracranial pressure is that it cannot explain the intracranial hypertension caused by 13-cis- and all-trans-retinoic acid. It is more likely that low RBP levels in the CSF in relation to the CSF retinol concentration lead to greater retinoic acid production and then increased transcription of retinoic acid-regulated genes. In an article from Smith and Goodman (5) in 1976, toxicity was proposed to occur when retinol is in excess of RBP and is delivered to tissues by lipoproteins. It was suggested that retinol delivered by lipoproteins disrupts cell membrane integrity (5). Recent research, especially studies of RBP-deficient mice (48), suggests that this early hypothesis put forward to explain biochemical effects underlying vitamin A toxicity is probably an oversimplification and incorrect. It is now thought that vitamin A toxicity arises primarily through changes in transcription rates of essential vitamin A-dependent genes and that these changes adversely influence cellular processes.

The study by Warner et al (1), the first to measure retinol and RBP in serum and CSF, represents a major contribution to our understanding of the role of vitamin A in IIH. We still know little about the relationship of RBP and retinol in serum to RBP and retinol in CSF, although a few studies have found a correlation (12,49). Many questions remain regarding vitamin A transport, metabolism, and function, especially in the CSF and brain. What are the differences between young and old, men and women, obese and thin? Given the tremendous growth of research on RBP in relation to insulin resistance and obesity, the future promises to teach us much about RBP and retinoids in health and disease.

TABLE 1. Summary of published retinol and retinol-binding protein (RBP) levels in patients with idiopathic intracranial hypertension as compared to control subjects

<table>
<thead>
<tr>
<th>Publication</th>
<th>Serum retinol</th>
<th>Serum RBP</th>
<th>Serum retinol/RBP</th>
<th>CSF retinol</th>
<th>CSF RBP</th>
<th>CSF retinol/RBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warner et al, 2007 (1)</td>
<td>High</td>
<td>Trend High</td>
<td>High</td>
<td>Normal*</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Tabassi et al, 2005 (12)</td>
<td>Normal</td>
<td>NM</td>
<td>NM</td>
<td>NM</td>
<td>NM</td>
<td>NM</td>
</tr>
<tr>
<td>Warner et al, 2002 (13)</td>
<td>Normal</td>
<td>NM</td>
<td>NM</td>
<td>High in some</td>
<td>NM</td>
<td>NM</td>
</tr>
<tr>
<td>Selhorst et al, 2000 (11)</td>
<td>Normal</td>
<td>High in some</td>
<td>NR</td>
<td>NM</td>
<td>NM</td>
<td>NM</td>
</tr>
<tr>
<td>Jacobson et al, 1999 (10)</td>
<td>High</td>
<td>NM</td>
<td>NM</td>
<td>NM</td>
<td>NM</td>
<td>NM</td>
</tr>
</tbody>
</table>

CSF, cerebrospinal fluid; NM, not measured; NR, not reported.

*Controlled for body mass index.

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Retinol-Binding Protein and Retinol Analysis in Cerebrospinal Fluid and Serum of Patients With and Without Idiopathic Intracranial Hypertension

Judith E. A. Warner, MD, Alexander J. Larson, BA, Prakash Bhosale, PhD, Kathleen B. Digre, MD, Courtney Henley, MD, Stephen C. Alder, PhD, Bradley J. Katz, MD, PhD, and Paul S. Bernstein, MD, PhD

Background: Several studies have implicated vitamin A-related compounds in the pathogenesis of idiopathic intracranial hypertension (IIH). The goal of this study was to compare cerebrospinal fluid (CSF) and serum concentrations of retinol and retinol-binding protein (RBP) in subjects with and without IIH.

Methods: CSF and serum samples were collected from 87 subjects. The study population was composed of subjects with IIH (IIH group, n = 28), subjects with non-IIH neurologic conditions (neurology controls, n = 42), and subjects undergoing preoperative lumbar puncture but with no known neurologic conditions (anesthesia controls, n = 17). RBP levels (nM) were determined using radial immunodiffusion, and retinol levels (nM) were determined using high-performance liquid chromatography.

Results: The retinol/RBP ratio was greater in CSF than in serum, especially in subjects with IIH.

Conclusions: The finding of increased levels of unbound retinol in the CSF of subjects with IIH provides further evidence that vitamin A may be involved in the pathogenesis of IIH. Comparative statistical analyses revealed multivariate relationships that demonstrate the need to further investigate correlations between vitamin A and RBP levels in CSF and serum.

Diabetic intracranial hypertension (IIH), also known as pseudotumor cerebri, is a condition of increased intracranial pressure (ICP) with normal cerebrospinal fluid (CSF) composition. IIH is generally accompanied by headache and papilledema, which can cause progressive vision loss. Initially described in the 19th century (1), the underlying cause of IIH remains unknown. Careful clinical evaluation, including appropriate imaging studies, is used to eliminate other causes for the increased pressure and associated signs and symptoms. IIH is usually observed in otherwise healthy obese women in their childbearing years (2,3).

Intracranial hypertension associated with elevated levels of the essential nutrient vitamin A was first reported in 1954 and evaluated in detail in 1970 (4,5). Reports from dermatologic, oncologic, and other clinical settings describe intracranial hypertension associated with vitamin A intoxication (6–9).

In American diets, approximately 75% of vitamin A is derived from retinol and 25% from provitamin A carotenoids, particularly β-carotene (10). Dietary vitamin A is absorbed primarily as long-chain fatty acid retinyl esters that are stored in the liver and hydrolyzed in the lumen of the small intestine to produce retinol. Normally, retinol is bound to the plasma carrier retinol-binding protein (RBP) in a 1:1 ratio for transport through the circulation. Human RBP has a molecular mass of 21 kDa and a single binding site for retinol; it appears to mediate retinol entrance into cells (6). When not bound to RBP, vitamin A is toxic to cell membranes (11). A retinol/RBP ratio of >1 suggests the presence of free, unbound retinol, a potential toxin.
Retinol and RBP in IIH

RBP and transthyretin have been localized to the choroid plexus, a key site for delivery of vitamin A and other nutrients to the CSF (12–15). Little is known, however, about the normal relationships between retinol and RBP in CSF. One study showed elevated serum RBP in some individuals with IIH (16). Previous studies documented elevated serum (17) and CSF (17–19) retinol levels in some subjects with IIH. Excess serum retinol may be toxic to arachnoid villi and inhibit CSF resorption, leading to increased ICP. However, the absolute values of retinol in any setting are not useful without correlation with RBP. One needs to know the extent to which RBP is saturated by retinol to conclude that free retinol is present.

No study has yet compared CSF and serum concentrations of both retinol and RBP in individuals with and without IIH. We investigated possible correlations between retinol and RBP levels in subjects with IIH, in subjects with other neurologic conditions, and in subjects without known neurologic pathologic conditions. We postulated that the relationship between serum and CSF retinol and RBP values could provide further insight into their possible role in the etiology of IIH.

METHODS

Subjects

The University of Utah Institutional Review Board (IRB) approved this project. Written informed consent was obtained from all study subjects before participation. Investigators obtained 1 mL of CSF and 2 mL of whole blood from subjects with IIH, as well as from subjects who either had other neurologic diseases (with or without increased ICP) or who had undergone lumbar puncture (LP) to exclude a diagnosis of IIH (“neurology controls”). Neurology controls did not have IIH based on normal ICP and fundus examination and, frequently, absence of signs of IIH. All LPs on these subjects were performed by the same person (J. W.), with pressure carefully measured when subjects were in the lateral decubitus position with legs extended and head in a neutral position immediately after CSF flow was established. Subjects with IIH and neurology controls, all of whom were consecutively recruited during ophthalmology or neurology clinic visits at the University of Utah Health Sciences Center, had complete documentation of their medical history and current medications. All subjects with IIH met modified Dandy diagnostic criteria for IIH (20).

Anesthesiology department personnel obtained study-specific written informed consent from the control subjects with no known neurologic diseases (“anesthesia controls”) before scheduled surgery in the Same-Day Surgery Unit of the University of Utah Health Sciences Center. Anesthesia controls had already consented to receive preoperative spinal anesthesia. Most of the LPs in this group were performed by the same person (C. H.), with pressure measured in the lateral decubitus position.

All analyses were performed on new subject specimens. Specimens used in prior studies at the Moran Eye Center (18) were not included in this study.

Sample Preparation

Serum for all samples was extracted from whole blood by centrifugation at 2,500 rpm for 5 minutes. CSF and serum samples were protected from light exposure, which could have altered the retinol concentration. All samples were stored at −76°C until analysis.

RBP Measurement

RBP levels were measured using a NANORID radial immunodiffusion (RID) kit (The Binding Site Limited, Birmingham, England), which was calibrated for serum with a 1:20 [serum-7% bovine serum albumin (BSA)] dilution. CSF was concentrated 40X and applied in 5 μL quantities to immunodiffusion plate wells using a micropipette. After sample application, the lid of the RID plate was tightly closed, and the plate was incubated at room temperature (20–24°C) in an airtight container for 96 hours. Incubation involved RBP (antigen) migrating from a cylindrical well through an agarose gel containing antibody to RBP. Antigen-antibody complexes formed a precipitin ring; concentration was determined by ring diameter measurement.

Retinol Measurement

For protein precipitation 250 μL CSF was treated with 250 μL methanol. Retinol was then extracted using 250 μL hexane containing 0.05% butylated hydroxytoluene (BHT) (w/v). Single step extraction was sufficient for 90% extraction of retinol; the extraction was then repeated to obtain a 500 μL sample. The retinol level in each CSF sample was measured by high-performance liquid chromatography (HPLC), using a DYNAMAX-60A silica column (Ranin Instrument, Emeryville, CA). Samples were eluted isocratically at a flow rate of 1.0 mL/min with a mixture of 10% 1,4-dioxane (v/v) in hexane on a Waters HPLC system (Waters Corporation, Milford, MA) with single wavelength detection at 325 nm. Additional details concerning this methodology have been published elsewhere (10,18).

For serum retinol analysis, the HPLC equipment (Thermo Electron, San Jose, CA) had an autosampler, two-channel solvent degasser, binary gradient pump, and UV-visible photodiode array detector. The vitamin A peak on each system’s chromatogram was quantified by external standardization against synthetic all-trans-retinol. Peak identities were confirmed by photodiode array (PDA) spectra.
and by coelution with authentic standards. Retinyl esters in CSF were never present in greater than trace amounts.

Statistical Methods

Data were entered into Microsoft Excel 2003 (Microsoft, Seattle, WA) and imported into SPSS 14.0 for Windows (SPSS Inc., Chicago, IL) for analysis. Comparisons were made among the IIH, neurology control, and anesthesia control groups using independent samples t tests, χ² tests, and one-way analysis of variance. Serum and CSF RBP and retinol levels and the ratio of retinol (nM) to RBP (nM) were compared among groups using one-way analysis of variance. Where parametric assumptions were violated, Wilcoxon rank-sum and Kruskal-Wallis tests were used. Analysis of covariance, using the general linear model, was used to adjust, respectively, for age, sex, body mass index (BMI), opening pressure (OP), and use of vitamins, thyroid medication, and estrogens. Multiple linear regression was used to estimate the association between age and total protein, controlling for IIH status. For all analyses, α was set at 0.05. Previous studies from the authors and others provided normal reference ranges for serum and CSF retinol and RBP (16-18,21-24). Statistical analyses were performed by a biostatistician (S. C. A.).

RESULTS

Table 1 summarizes the demographics of our three subject groups. There were more women in the IIH group, and the mean age of the IIH group was less than that of the other two groups. These demographics are consistent with the fact that the majority of patients with IIH are premenopausal women. The mean BMI of the IIH group was higher than mean BMI in the other two groups. The mean OP of the IIH group, 328.6, exceeded the 250 minimum value required for diagnosis of IIH according to Modified Dandy Criteria (3). Four subjects with IIH had normal ICP recorded in this study but had had a prior diagnostic LP showing elevated ICP. Some neurology control patients had elevated ICP due to conditions such as venous thrombosis, renal failure, and parathyroid disorders.

Data comparing RBP, retinol, and the retinol/RBP ratio in serum and CSF of subjects in the three groups are presented in Table 2. IIH subjects had higher serum and CSF retinol levels than did neurology controls or anesthesia controls (P = 0.001 and P = 0.05, respectively). Conversely, CSF RBP levels were lowest in the IIH group (P < 0.001). Serum RBP levels were highest in the IIH subjects, but this difference was not statistically significant (P = 0.07). The serum retinol/RBP ratio ranged from approximately 0.40 to 0.55, whereas the CSF retinol/RBP ratio was > 1.0 in all three groups. In both serum (P = 0.05) and CSF (P = 0.001), IIH subjects had the highest retinol/RBP ratio. We analyzed our data for differences in retinol and RBP in subjects with newly diagnosed IIH vs previously treated subjects with IIH and found no significant differences. One study subject in the IIH group was removed from the CSF retinol and CSF retinol/RBP ratio analyses because of extreme values, but results remained statistically significant.

Because of limitations imposed by the IRB, CSF protein and cell counts were not measured in the anesthesia controls. Consequently, comparisons using these data were not possible. However, in comparing IIH subjects with neurology controls, CSF total protein increased with age [β = 0.49 (slope of curve), P = 0.001] and showed a trend toward being lower in the IIH group [β = 8.69 (difference between the two groups), P = 0.07]. This is consistent with other research findings.

We also evaluated the potential confounding factor of CSF contamination with red blood cells (RBC). We found no significant association between CSF RBC and retinol levels (data not shown). Our results maintained statistical significance even if the IIH subject with markedly elevated

| TABLE 1. Demographics of subjects with idiopathic intracranial pressure (IIH), non-IIH neurologic conditions (Neurology Controls), and undergoing lumbar puncture for surgical procedures (Anesthesia Controls) |
|-----------------|-----------------|-----------------|-----------|
|                 | IIH (n = 28)    | Neurology       | Anesthesia |
|                 | controls (n = 42) | controls (n = 17) | Controls |
| Age, mean (SD) | 32.1 (10.2)     | 44.8 (16.4)     | 59.5 (19.7) | <0.001 |
| Female, f (%)  | 26 (92.9)       | 22 (52.4)       | 9 (52.9)   | 0.001 |
| Body mass index, mean (SD)* | 36.5 (8.7) | 29.0 (5.7) | 28.3 (4.2) | <0.001 |
| Opening pressure (mm CSF), mean (SD) | 328.6 (86.5) | 189.4 (62.7) | 192.8 (77.9) | <0.001 |
| Vitamins, f (%) | 3 (10.7)        | 14 (33.3)       | 6 (35.3)   | 0.07 |
| Thyroid medications, f (%) | 2 (7.1) | 1 (2.4) | 1 (5.9) | 0.62 |
| Estrogens, f (%) | 6 (21.4) | 3 (7.1) | 1 (5.9) | 0.13 |

*Calculated by the formula [weight in pounds × (39.37²)] / [2.2 × (height in inches²)].

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TABLE 2. Comparison of levels of retinol-binding protein (RBP), retinol, and retinol/RBP ratios in serum and cerebrospinal fluid (CSF) in three subject groups

<table>
<thead>
<tr>
<th></th>
<th>IIH (n = 28)</th>
<th>Neurology controls (n = 42)</th>
<th>Anesthesia controls (n = 17)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum RBP (nM)</td>
<td>3668.3 (1599.9)</td>
<td>3465.7 (1710.5)*</td>
<td>2545.6 (817.1)†</td>
<td>0.07</td>
</tr>
<tr>
<td>Serum retinol (nM)</td>
<td>1834.9 (768.0)</td>
<td>1662.8 (846.0)*</td>
<td>972.5 (380.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Serum retinol/RBP ratio</td>
<td>0.54 (0.19)</td>
<td>0.49 (0.19)‡</td>
<td>0.39 (0.14)†</td>
<td>0.05</td>
</tr>
<tr>
<td>CSF RBP (nM)</td>
<td>6.9 (4.4)</td>
<td>12.4 (6.4)§</td>
<td>8.9 (3.3)†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CSF retinol (nM)</td>
<td>22.0 (60.3)$</td>
<td>12.4 (7.0)$‡</td>
<td>15.3 (5.7)$†</td>
<td>0.05‡</td>
</tr>
<tr>
<td>CSF retinol/RBP ratio</td>
<td>2.89 (6.92)$</td>
<td>1.14 (1.27)$*</td>
<td>1.84 (0.76)$†</td>
<td>0.001‡</td>
</tr>
</tbody>
</table>

Values are mean (SD).

* n = 40.
† n = 16.
‡ n = 39.
§ n = 26.
¶ Kruskal-Wallis test.
\( n = 27. \)

retinol was removed from analysis. This subject’s spinal fluid was initially bloody and then cleared during the LP, with the aliquot used for study being the last tube collected.

When comparisons across study subject groups were controlled for BMI, serum RBP (P = 0.050), serum retinol (P = 0.001), CSF RBP (P = 0.001), and the CSF retinol/RBP ratio (P = 0.032) were significantly different, whereas the serum retinol/RBP ratio (P = 0.090) and CSF retinol (P = 0.195) were not.

**DISCUSSION**

We have confirmed previously reported ranges of serum and CSF retinol and RBP concentrations in subjects with and without IIH (16–19). Furthermore, our results are consistent with previous studies that documented higher serum retinol and RBP values in individuals with IIH than in others (16,17). Previously reported IIH-associated elevations of serum and CSF retinol are made more compelling by our findings, which for the first time compare and relate all four levels to each other in the same subject population. In addition, our study shows not only that CSF retinol is elevated, but also that the compensatory elevation of RBP is less than expected. In fact, CSF RBP was lowest in the subjects with IIH. The resulting retinol/RBP ratio of >1.0 in the CSF of our subjects with IIH suggests the presence of unbound toxic retinol that might interfere with pressure regulation. Furthermore, the presence of unbound retinol in the CSF supports the hypothesis that vitamin A may be involved in the pathogenesis of IIH.

Previous studies document the fact that CSF RBP and CSF protein increase with age (23,25). This increase was confirmed in our subject population. One could speculate that high CSF protein, concomitant with high CSF RBP, may protect older individuals from development of IIH. It is also possible that there is another carrier protein in the CSF, in addition to RBP, that would nullify the toxic effects of the measured retinol excess. Thus far, no other carrier protein has been identified; but research in this area could prove to be fruitful.

Our subject groups were understandably different demographically because of the strong association between IIH, obesity, youth, and female sex. However, when we controlled for BMI, the observed relative elevation of retinol compared with RBP in CSF persisted, although the absolute elevation of retinol lost its statistical significance. In serum, the elevations of retinol and RBP persisted, whereas the ratio was no longer significantly different. These findings suggest again that the unbound retinol in the CSF may be toxic because of insufficient RBP transfer into CSF, excessively dilute CSF with relatively low RBP, or other potential mechanisms. The regulatory system in serum may be more tightly controlled even in subjects with IIH.

We recommend that future research be conducted with a larger sample size, which would permit investigation of possible influences of vitamin supplements, thyroid medication, and estrogen use on retinol and RBP levels. In our study, use of these medications did not differ significantly in the three groups. Vitamin use was lower in our subjects with IIH. Although we adjusted for these variables, our sample size was not sufficient to optimally address their impact on results. A larger sample size would also permit further investigation of the wide range of CSF retinol levels we observed in the IIH subject population of this study and our previous study (18). This broad range of CSF retinol levels raises the question as to whether there are some subgroups in which retinol plays a role in IIH and
other subgroups in which retinol does not assume such a role. Further analysis of these hypothetical subgroups may provide useful results.

The problem of finding appropriate age-matched control subjects willing to undergo LP solely for research purposes limits this and other studies. To procure optimal data for comparisons, it will be necessary to obtain reliable OP measurements and to determine CSF protein levels and cell counts from sex-, BMI- and age-matched controls.

Comparative analyses of our IIH, neurology control, and anesthesia control groups demonstrated complex multivariate relationships. Further study is required to investigate the correlations we have identified between IIH and both CSF and serum levels of retinol and RBP. Additional studies to determine a possible relationship between retinol saturation of RBP in the CSF and the development of IIH may be critical to further understanding of the pathophysiology and treatment of this disease.

Acknowledgments

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REFERENCES


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The Prevalence of Relative Afferent Pupillary Defects in Normal Subjects

Helmut Wilhelm, MD, Tobias Peters, Holger Lüdtke, PhD, and Barbara Wilhelm, MD

**Background:** Observational and pupillographic studies of small numbers of normal subjects have shown that a small (<0.3 log units) relative afferent pupillary defect (RAPD) is present in a minority. We have extended the investigation of the prevalence of RAPD to a larger number of normal subjects.

**Methods:** A total of 102 subjects were examined by observation and pupillography. The swinging flashlight test was performed using neutral density filters for quantification. During the pupillographic procedure, light-emitting diodes were placed in front of each eye, alternately flashing for 2.5 seconds with a 0.5 second break. A binocular real-time pupilometer recorded the direct and consensual pupillary responses. After artefact detection and removal, the amplitudes of pupillary response were determined and plotted against stimulus intensity. The means of the direct and the consensual responses were used for automated calculation of RAPD.

**Results:** By observation, there was no RAPD in 87 (85%) subjects; there was an RAPD of 0.15 log units in 13 (13%), and an RAPD of 0.3 log units in 2 (2%). By pupillography, there was an RAPD of 0.07 log units in 53 (52%) subjects, an RAPD between 0.08 and 0.22 log units in 43 (42%) subjects, and an RAPD between 0.23 and 0.39 log units in 6 (6%) subjects.

**Conclusions:** Observation and pupillographic measurements of the swinging light test in a large normal subject cohort has confirmed that an RAPD is present in a small minority but that it does not exceed 0.39 log units. The RAPD in these subjects may be explained by inaccuracy of measurement or by asymmetries in the connections between visual pathways and pretectal nuclei in the midbrain.

(A relative afferent pupillary defect (RAPD) generally indicates a unilateral or asymmetric disorder of the retina or optic nerve (1–5). The question of whether an RAPD may be present in a completely healthy subject has been addressed in observational and pupillographic studies (6–8). In an observational study (6) using the swinging flashlight test in 4,208 subjects, an ophthalmologist found that 49 had an RAPD, and in 2 of these no appropriate pathologic condition could be identified with further workup. However, the criterion for an RAPD in that study was “pupillary escape,” or dilation of the pupil on the involved side when the “swinging light” returns to it from the other side. This criterion precludes sensitivity for small RAPDs. Cox (9) found pupillary escape in only 1 of 14 patients who were expected to have an RAPD and concluded that the initial constriction is a more sensitive criterion (10), one that is less influenced by the presence of physiologic anisocoria (11). Most clinicians look for differences in the initial constriction and for pupillary escape. How many normal subjects would have an RAPD by this method of evaluation is not known.

In cases of physiologic anisocoria, it may also be necessary to compare direct and consensual responses of the same eye. Contraction anisocoria (12), that is differences between direct and consensual responses, might influence the determination of an RAPD. An optimal observational method of determining an RAPD therefore includes determination of both direct and consensual responses.

However, in detection of small RAPDs, pupillographic methods are preferable to observation, as the results are not dependent on the examiner's subjective impression. Moreover, an unlimited number of stimulations can be tested and evaluated in the same patient. In a pupillographic study by Kawasaki et al (7), the investigators tested for short-term fluctuation of a pupillographically determined RAPD in 10 healthy subjects and found that the variability depended on the number of stimulus pairs applied. The confidence interval was 0.4 log units if 10 stimulus pairs were tested and only 0.1 log units if 100 stimuli pairs were used. With a stimulus configuration most comparable to ours, an RAPD of 0.3 log units was found in 1 subject. In a second pupillographic study, Kawasaki et al (8) examined RAPD fluctuation in 17 healthy subjects over 3 years and found a maximal RAPD of 0.3 log units in 7 of...
68 measurements. In a third pupillographic study, Volpe et al (13) compared 13 healthy volunteers with patients who had different amounts of RAPD. They could not distinguish normal subjects from patients with RAPDs of 0.3–0.6 log units.

These studies point out the fact that an RAPD of approximately 0.3 log units may be found in normal subjects, but the number of subjects examined in these studies was small. We report the results of examining 102 normal subjects by observation and by pupillography.

METHODS

Subjects
A total of 102 normal subjects (41 men and 61 women) aged between 12 and 59 years (median 29 years) took part in the study. They were recruited from the hospital and among friends of the authors and gave written consent. By history and basic ophthalmologic examination, ocular disorders affecting the pupillary light reflex or causing unilateral afferent defects were excluded. For each subject, visual acuity, slit lamp examination, and direct funduscopic examination of the optic disc and macular region and cover test were performed. Patients with neurologic disorders, severe head trauma, or diseases that could have led to cerebral ischemia were excluded. None of the subjects were using medication that could affect pupillary function.

Classic Swinging Flashlight Test
The swinging flashlight test was performed on each patient. The criterion applied was the speed and amplitude of the initial pupillary constriction. Pupillary escape was not observed in any of the subjects. After a swinging flashlight test with at least five cycles using an indirect ophthalmoscope as a light source was performed, a 0.15 log unit neutral density filter was sequentially placed in front of each eye. If there was no RAPD visible or if the RAPD appeared always on the side with the filter, an RAPD of 0 was noted. An RAPD of 0.15 log units was noted if an RAPD was seen without the filter and if the RAPD disappeared when the 0.15 log units filter was held in front of the non-RAPD eye. If the RAPD was present even with a 0.15 log units filter before the non-RAPD eye, the test was repeated with a 0.3 log units filter. An RAPD of 0.3 log units was noted if this filter eliminated the RAPD; an RAPD of 0.15 log units was noted if the RAPD was reversed. Testing with superimposition of 0.3 and 0.15 log units filters always showed an RAPD on the side of the filters. If the 0.15 log units filter could not eliminate an RAPD, perimetry using the Tübingen automated perimeter was performed to exclude subclinical optic nerve disease. The same was done when an RAPD of 0.2 log units or more was measured by pupillography.

Pupillographic Swinging Flashlight Test (SWIFT by Ocuserv Tübingen)
A binocular pupillographic system based on an infrared video technique by means of a charge-coupled device (CCD) camera with a time resolution of 25 Hz and a spatial resolution of 0.24 mm was used. Details of this method have been described extensively previously when the system was used to detect RAPDs in patients with optic neuropathies (14). The light conditions were mesopic (≈0.5 cd/m² background illumination of the walls of the laboratory). The patient’s head was placed on a chin rest 80 cm away from the instrument, which was equipped with a telephoto lens. The pupillary light reflex was elicited by means of two arrays of 12 green light-emitting diodes placed in front of each eye and providing a corneal illumination of 60–80 lux depending of the distance between diodes and the patient’s eye. Seven circles of measurements were performed with variable light intensities (Table 1). Each circle comprised 6 stimuli for each eye. Altogether 42 pairs of stimuli were applied in each subject. Each light stimulus lasted 2.5 s followed by a 0.5 s pause. The whole measurement lasted 252 s. We calculated the means of the direct and consensual constrictions. Measurements with artefacts (blinks) were discarded (Fig. 1). Thereafter the mean differences in response amplitudes between stimulation of the left and right eyes were plotted against the logarithm of the light stimulus difference and fitted linearly (Fig. 2). The intersection with the x-axis indicated the RAPD in logarithmic units. The system was tested with artificial RAPDs evoked by neutral density filters and could reliably reproduce RAPDs of 0.15 and 0.3 log units.

TABLE 1. Stimulus protocol used with the automated swinging flashlight test*

<table>
<thead>
<tr>
<th>Filter density (log unit)</th>
<th>Right eye relative intensity</th>
<th>Left eye relative intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>No filter</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>0.3 left</td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td>0.3 right</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>0.6 right</td>
<td>25</td>
<td>100</td>
</tr>
<tr>
<td>0.6 left</td>
<td>100</td>
<td>25</td>
</tr>
<tr>
<td>1.0 left</td>
<td>100</td>
<td>10</td>
</tr>
<tr>
<td>1.0 right</td>
<td>10</td>
<td>100</td>
</tr>
</tbody>
</table>

From Wilhelm et al (14).

*To calibrate the instrument, the brightness of the light-emitting diode arrays was measured exactly. These values usually differed in small amounts from the ideal values shown in this table (for example, 96 instead of 100). For calculation of the RAPD, those exact values were used rather than the “ideal” values listed in this table. The total corneal illumination at 100% brightness was between 60 and 80 lux depending on the individual orbital anatomy.
Results

The clinical swinging flashlight revealed no RAPD in 87 (85%) of 102 subjects, an RAPD of 0.15 log units in 13 (13%) subjects, and an RAPD of 0.3 log units in 2 (2%) subjects. Higher RAPDs did not occur. The overall mean of the observationally measured RAPD of all subjects (independent of the side of the RAPD) was 0.02 log units, 0.07 log units below the pupillographic mean.

Pupillographic results were similar to the clinical findings (Fig. 3). An RAPD of 0.07 log units or less was present in 53 (52%) subjects, between 0.08 and 0.22 log units in 43 (42%) subjects, and between 0.23 and 0.39 log units in 6 (6%) subjects. The maximum RAPD was 0.39 log units, found in one subject. The mean RAPD was 0.09 log units if the amount of RAPD was taken independently from its laterality. If a right RAPD was calculated as positive and a left RAPD as negative (Fig. 3), the RAPD was +0.02 with a SD of ±0.12. Among our subjects, 95% had results in the range between +0.25 and 0.25 log units (positive value means RAPD on right; negative value means RAPD on left). No visual field defect was found pupillographically in the subjects with RAPD ≥ 0.2 log units. There was a weak correlation between the RAPD measured by observation and by pupillography ($R^2 = 0.056, P < 0.03$) (Fig. 3).

Discussion

This study has confirmed the results of former studies on the prevalence of an RAPD in normal subjects. An RAPD of 0.3 log units, the threshold of detectability by the swinging light test performed with good technique, was present in fewer than 2% of 102 subjects by careful observation and pupillography. An RAPD of >0.39 log units was not found. Whether the prevalence of RAPDs within a normal population older than 60 years would be higher cannot be answered by our study.

Short-term fluctuation and inaccuracy of measurement might explain a certain variability of the results at RAPDs of 0.15 log units, but it is unlikely that an RAPD of 0.3 log units measured pupillographically would be explained by inaccuracy of measurement alone. Comparing the present study to the first study of Kawasaki et al (8), the application of 42 pairs of stimuli in each subject should have produced short-term variability slightly below 0.2 log units. Kawasaki et al (8) observed this variability with 40 pairs of stimuli.
An RAPD in normal subjects that exceeds 0.15–0.2 log units is probably an expression of natural fluctuations in the pupillary system. Perhaps it is the afferent counterpart to physiologic anisocoria. In the study of Kawasaki et al (8) on long-term RAPD variability, there were subjects who had randomly reversing RAPD between the two eyes, but in 8 of these 17 subjects, the RAPD was always on the same side (8). This phenomenon might be due to diffuse asymmetry of retinal light sensitivity. Congenital or acquired subclinical lesions are a second possible explanation. A third explanation may be asymmetry within the connecting pathways between the afferent visual system and the pretectal area. Some patients with lesions in the pulvinar-pretectal area show an unequivocal RAPD without any measurable visual deficit (15–18).

On the basis of our study and previous reports, an RAPD > 0.3 log units (11) is likely to be an expression of a substantial lesion of the afferent pathways and requires further evaluation. An RAPD of <0.3 log units in an otherwise healthy subject with normal visual fields may be accepted as a normal finding.

Pupillographic measurement of the RAPD may be helpful in unclear cases and clinical trials (19). It has the advantage of avoiding mistakes that occur in observational methods, especially different light exposure times for the two eyes. Automated evaluation removes examiner bias and the problems related to comparison of examinations of different clinicians. Binocular measurement of the pupils reduces the influence of physiologic and contraction anisocoria on the results. Awareness of these problems motivated the development of an automated procedure and device (SWIFT by Ocuserv Tübingen) (14). The aim was to come close to the clinically applied swinging flashlight test by choosing an illumination time of 2.5 s and an alternating time of 0.5 s. Kawasaki et al (7) tested different combinations of illumination and alternating times and could not demonstrate a clear preference. However, they showed that steps smaller than 0.3 log units did not increase the accuracy of the measurement. Because of its stepwise noncontinuous characteristics, the gray filter method may produce a slight underestimation of the clinical RAPD because results between 0.15 and 0.3 log units are put on 0.15 log units and results between 0 and 0.15 are put on 0 log units. This result is expressed by a lower mean of the observational RAPD than of the pupillographic RAPD.

The poor correlation between observationally and pupillographically assessed RAPDs in this study is puzzling. However, the range of RAPDs found in our subjects was very narrow, and the vast majority of the data points clustered near 0. Therefore, one could hardly expect a good correlation. The two subjects with pupillographically measured RAPDs > 0.3 log units had no RAPD when examined by observation, which may indicate that natural variability plays a major role.
REFERENCES


Spatial Processing in Bálint Syndrome and Prosopagnosia: A Study of Three Patients

Jason J. S. Barton, MD, PhD, FRCPC, George L. Malcolm, MA, and Rebecca L. Hefter, MSc

Background: Spatial analysis may be subdivided into between-object and within-object spatial coding. We investigated the contribution of various visual cues to grouping processes that might determine whether single or multiple objects were perceived and therefore which type of spatial coding would be used for a stimulus.

Methods: We asked three patients to make shape judgments with a series of displays showing triangular arrangements, moving from more implicit triangles defined by separate objects at the apices (between-object spatial coding) to more explicit triangles with line edges or surface texture (within-object spatial coding).

Results: In two patients with prosopagnosia, within-object spatial judgments were impaired, whereas between-object spatial judgments were normal. In a patient with Bálint syndrome, the reverse pattern was obtained. Surface texture but not outline closure led to mandatory within-object coding in the prosopagnosic patients, whereas outline or surface texture was sufficient to support intact within-object spatial judgments in the patient with Bálint syndrome. Illusory contours were ineffective in promoting within-object coding in either condition.

Conclusions: These findings support the existence of parallel representations of space for within-object and between-object processing and reveal the efficacy of different cues in determining which representation is potentially accessible.

belonging to separate objects? In the context of spatial representation, what are the visual elements that promote a within-object over a between-object representation?

Examining a neuropsychologic sample may be particularly revealing on this point. By using stimuli that vary in the cues that pit one perceptual representation against the other, we can determine which visual properties are sufficient to effect a transition from between-object to within-object representation. In patients with selective deficits of one form of spatial representation but not the other, this transition should be marked by a performance transition between success and failure on a spatial task using these stimuli.

We devised a task using a series of very similar triangular configurations that varied in the elements that defined the triangle. At one extreme, these elements could promote the perception of separate objects at the triangle’s apices; at the other they could promote the perception of a single triangular object. By systematically varying the elements in the stimulus, we wished to discover the features that were most likely to create a transition from within-object to between-object coding. We examined three patients’ abilities on this task. Two had occipitotemporal lesions causing prosopagnosia, a selective defect in face recognition, which we showed to be associated with failures in perceiving within-object spatial relations. One had occipitoparietal lesions causing Bálint syndrome.

METHODS

Subjects

Subject 005 is a 59-year-old man examined 10 months after a right medial occipitotemporal stroke. He has difficulty recognizing faces, more so for people met since or in the years just before his stroke but not for long-familiar friends. He complains of decreased brightness but not loss of color perception. He has topographagnosia. Snellen acuity was 20/20 in both eyes, and he has a complete left homonymous hemianopia. His eye movements were normal. Neuropsychologic testing revealed a verbal IQ of 150. He copied the Rey-Osterreith figure normally. He had memory difficulties, which were worse for nonverbal items. His Benton Face Recognition Test score was 35/54. Brain MRI showed a large right medial occipitotemporal infarct (Fig. 1).

Subject 010 is a 41-year-old man with bilateral posterior occipitotemporal lesions from a car accident 20 years earlier that caused a subdural hematoma. He had been cortically blind for a few weeks immediately after the event but his sight recovered partially. He now has prosopagnosia, some mild object agnosia, and complaints of partial dyschromatopsia. Snellen visual acuity is 20/20 in both eyes, and he has a right homonymous hemianopia. Eye movements are normal. MRI showed bilateral occipitotemporal and right frontal lesions.

Subject B.001 is a 48-year-old woman who had bilateral occipitoparietal infarctions from primary central nervous system vasculitis 5 months before testing. Examination at onset of the strokes showed a left inferior quadrantanopia, left hemi-neglect, inaccurate saccades with impersistence of fixation, and poor pursuit. She had optic ataxia with either hand and simultanagnosia, as tested with the Cookie Theft picture and other displays. Examinations over the following months showed a visual acuity of 20/40 in both eyes and resolution of the inferior quadrantanopia and hemineglect. She saw multiple items on the Cookie Theft picture but could not relate the elements to each other. Saccadic accuracy was better, and there was only mild misreaching to visual targets with the left hand. Recognition of single objects as tested with line drawings was normal.

Testing

Subjects sat facing an Apple Multiscan 1705 monitor (Apple Inc., Cupertino, CA) in standard dim room lighting at a viewing distance of approximately 57 cm. Experiments were run on a G4 Powermac (Apple Inc.) using Superlab 1.71 (Cedrus, Phoenix, AZ).

All stimuli were based on an equilateral triangle with sides of 6.1° (175 pixels). One apex was moved farther away from the other two, by 4, 6, or 8 pixels. The task was to indicate which apex was farther away. In our prior report, we showed that prosopagnosic subjects with or without hemifield defects (including subjects 005 and 010) could make accurate judgments of similar spatial distances between stimuli under time-limited viewing conditions (8). The six stimuli were designed to approximate a progression from between-object to within-object spatial coding (Fig. 2). The first stimulus (“Discs-Only”) consisted of three “Pac-Man”-like objects (discs of 2.5° diameter with wedges cut out) located at the apices of the triangle. Each disc had a different texture to foster classification as distinct objects and to promote between-object spatial coding.

The second stimulus (“Kanisza”) had the apical discs rotated 180°, so that the wedges defined an illusory triangle, with the discs all possessing the same texture. The illusion is compelling, and the distances involved in our stimuli are within the range of human perception of illusory contours (10). In the third stimulus (“Line+Discs”), the triangle was made explicit by a line drawing. In the fourth stimulus (“Surface+Discs”), the surface of the triangle was filled with a texture. The fifth and sixth stimuli (“Line-Only” and “Surface-Only”) were similar to the third and fourth, except that the apical discs were absent. These last stimuli were most likely to involve within-object spatial coding. For each degree of change, we presented 18 trials,
for a total of 324 trials. These were presented in random order in 3 blocks of 108 trials, with each block containing two stimulus types; the order of blocks was also randomized. Viewing duration was limited to 1 second per trial.

Subjects 005 and 010 performed this experiment. We tested 10 control subjects (5 men and 5 women) ranging in age from 17 to 43 years. For each of the six stimuli we chose the two levels of change that, averaged together, yielded a mean accuracy between 90% and 95%. We used...
Prosopagnosia and Bálint Syndrome

For subject B.001, we altered the task and stimuli slightly. Our concern was that the instructions in the above paradigm might promote a strategy of inspecting each apex and would require the subject to assign a spatial label to the target, both of which could be a methodologic limitation in someone with both simultanagnosia and deficient saccadic targeting. Rather, we devised a version that used both equilateral triangles and “asymmetric triangles,” with one of the two lower apices displaced farther away from the other two. For this test we used the same size triangular configurations, with sides of 175 pixels (6.1°), but with slightly easier changes to detect, using apical shifts of 24, 26, or 29 pixels. A third of the trials showed an equilateral triangle and the rest showed an asymmetric triangle, with equal numbers of asymmetric triangles having the right vs left lower apex displaced outward. The subject was asked to indicate whether the triangle on a given trial was symmetric or asymmetric around a vertical axis. A similar series of six different types of triangular stimuli were used, in separate blocks, with randomized order. Eighteen trials were shown for each of the six types of stimuli, for a total of 108 trials. Viewing duration was not limited. One male control subject aged 45 performed this experiment, confirming that the task was easily completed with perfect accuracy for all six stimuli.

RESULTS

Prosopagnosic subjects 005 and 010 performed well with the Discs-Only, Kanisza, and Line + Discs stimuli (Fig. 3). Subject 005 had a borderline low performance for the Discs-Only stimulus, but otherwise performance was in the normal range. Performance for both subjects decreased with the remaining three stimuli: Surface + Discs, Surface-Only, and Line-Only. This decline was more dramatic for subject 010, who had bilateral occipitotemporal lesions, than for subject 005, who had a unilateral right occipitotemporal infarct. For subject 005, the score for the Surface + Discs condition was just within the normal range, due in part to a larger variance in the normal scores for this stimulus compared with other stimuli. The most dramatic contrast in subject 010 was between the Line + Discs and Surface + Discs stimuli. Whereas his accuracy with the Line + Discs was a normal, near-ceiling 92%, adding surface texture caused his score to plummet to a below-threshold level of 61%.

The patient with Bálint syndrome had a dramatically different performance pattern. She performed flawlessly when a line or surface was explicitly defined but performed at chance with the Discs-Only and Kanisza conditions. Although these were easier tests than those used for the prosopagnosic patients (to mitigate potential problems with
spatial attention and localization in Bálint syndrome), the reversal in results compared with the prosopagnosic data cannot be attributed solely to test difficulty, as the six tests had equivalent spatial manipulations and were performed at a similar high level by an age-matched control subject. Rather, they indicate a fundamentally different pattern of spared vs affected abilities than that in prosopagnosia.

**DISCUSSION**

Our results support the existence of distinct between-object and within-object spatial representations, with the former supported by occipitoparietal processing and the latter by occipitotemporal processing. The patient with Bálint syndrome from occipitoparietal lesions was impaired when evaluating a triangle defined solely by distinctly separate discs located at its apices and normal when evaluating a triangle defined by outlines or surface texture. In contrast, the patients with prosopagnosia from occipitotemporal lesions had the opposite performance pattern. They were impaired when evaluating a triangle defined by outlines or surface texture and normal when evaluating a triangle defined by discs at its apices. Their deficit with evaluating the metrics of object spatial structure is consistent with our prior documentation of their impaired perception of the spatial relations of facial features (11–14).

Dissociations between within-object and between-object spatial coding have been described in other disorders. Reversing patterns of hemi-neglect have been described, for example (4–6). When viewing words, these patients omit or substitute the first letter of words (left-sided within-object neglect) yet ignore words on the right side of the page (right-sided between-object neglect). When naming the letters of words they neglect the right-sided letters, even though they make left-sided errors when reading the word. With abstract patterns, the side neglected depends upon whether the pattern’s elements are grouped into a single object. Other studies have since described patients with within-object but not between-object neglect or vice versa, supporting a dissociation between these processes (15).

The parallel existence of between-object and within-object spatial coding has been linked to the concept of two processing streams in cerebral cortex (4). Ventral occipitotemporal cortex is involved in object recognition (1), and within-object spatial coding may be important in the specifying object structure. Between-object spatial coding is relevant to spatial localization and direction for action (16), functions assigned to the dorsal occipitoparietal cortex. A few studies have provided neuropsychologic evidence supporting these links. The impairment of a patient with bilateral parietal lesions in comparing the spatial length of two objects was ameliorated if these could be grouped into a single structure (7), implying normal within-object but abnormal between-object coding. Reaction time studies have shown faster processing for counting individual letters than for reading words in two patients with ventral occipitotemporal lesions and vice versa in two patients with dorsal occipitoparietal lesions (15). Our accuracy data clearly complement these findings, with impaired analysis of relations between separate objects.
in Bálint syndrome and impaired analysis of relations in a single form in prosopagnosia, a selective type of object agnosia.

Our experiment also provides some additional data on the binding or grouping process involved in segmenting elements into objects. Aspects such as continuity, collinearity, and closure within stimuli promote low-level grouping of elements (17). Our triangular stimuli pitted some of these features in competition with the presence of separable individual elements (the discs at the triangle's apices). In our prosopagnosic patients, collinearity in the Kanisza stimulus and closure in the Line + Discs stimulus were not sufficient to override the presence of the discs, which allowed for normal between-object processing. However, making the surface explicit with texture (Surface + Discs) did lead to a dramatic reduction in accuracy, especially in subject 010. We thus speculate that, in the presence of distinct separable elements such as the discs, explicit surface representation but not just collinearity or closure leads to a mandatory induction of grouping into a single object, which in our patients had the consequence of failure of spatial coding within this object.

In the patient with Bálint syndrome, accuracy was flawless as long as outline or surface texture was present. One might have expected her to fail on the stimulus that combined the discs with an outlined triangle (Line + Discs), as the prosopagnosic subjects had performed well with this stimulus. The success of the prosopagnosic subjects suggests that they were able to access between-object representations to make perceptual judgments about the Line + Discs stimulus. However, the patient with Bálint syndrome also succeeded with this stimulus, suggesting that she was able to access within-object representations for the Line + Discs stimulus. This stimulus thus appears to be a flexible "hinge" point, where within-object or between-object spatial representations are equally accessible. In the competition between these two spatial representations, patients with one weakened representation can access the remaining normal representation, whichever one it is. Once the triangular surface is filled in with texture, though, access to between-object spatial coding is no longer possible, and the stimulus is mandatorily processed by within-object spatial coding, given the prosopagnosic data. Given the data from the patient with Bálint syndrome, the separate discs cannot access within-object representations and must be processed by a between-object spatial coding.

The results from both types of patients agree on the failure of illusory contours to promote a grouping effect sufficient to counteract between-object spatial representations. Although the illusion of a single triangle is a powerful one, the prosopagnosic subjects continued to process the spatial relations of the illusory triangle efficiently, whereas the patient with Bálint syndrome failed to do so, indicating the primacy of between-object spatial representations with this stimulus despite the vivid illusion. Others have argued that illusory contours are seldom encountered naturally (18), and perhaps this ecologic infrequency limits the power of their contribution to internal decisions about spatial representation. Nevertheless, illusory contours emerge at relatively early levels in the neurophysiologic hierarchy, with neuronal discharges at illusory edges occurring in V2 (19). One could speculate that this finding implies that grouping effects are at least partly determined at even earlier levels of visual processing, perhaps even at V1, where illusory contours may actually be de-emphasized (20). Indeed there is some evidence for grouping processes that may affect the salience of object boundaries in monkey V1 (21,22). Whether these early processes are responsible for triaging spatial analysis to between-object vs within-object processing mechanisms deserves further investigation.

Acknowledgments
We thank D. Press for referring subject 005, M. Alexander for subject 010, and R. G. Robinson for subject B.001. S.-Y. Moon assisted with processing magnetic resonance images.

REFERENCES
Closely Spaced Stressful Life Events Precede the Onset of Benign Essential Blepharospasm and Hemifacial Spasm

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Background: The purpose of this study was to assess the possible role of major stressful life events, complicated grief, and depression in the pathogenesis of benign essential blepharospasm (BEB) and hemifacial spasm (HFS).

Methods: This was a case-control study involving 23 participants with BEB/HFS and 23 control subjects, comparing the frequency of major stressful life events, depression on the Beck Depression Inventory-II, and complicated grief on the Inventory of Complicated Grief.

Results: There was no difference in the rate of depression or complicated grief between participants with BEB/HFS (57%) and control subjects (48%). Participants with BEB/HFS experienced a significantly \( P = 0.0048 \) shorter time interval between two major stressful life events (median, 0.3 year) than did the control group (median, 3.0 years). The proportion of participants who had suffered two major stressful lifetime events separated by 1 year or less was significantly greater for participants with BEB/HFS than for control subjects \( P = 0.0007 \).

Conclusions: The onset of BEB and HFS was often preceded by a major lifetime stressor. The development of these conditions was significantly related to the number of stressful life events occurring within the preceding year rather than to the total number of stressful life events. Subjects who sustain closely spaced stressful life events may be at increased risk of developing BEB and HFS.

In 1947, Campbell and Keedy (1) published the first report of vascular compression of the facial nerve as a cause of hemifacial spasm (HFS). Microvascular decompression surgery for HFS was then reported by Gardner and Sava (2) and popularized by Jannetta (3). It is postulated that the facial nerve at the root entry zone becomes demyelinated due to mechanical stress from repeated pulsations of the vascular loop, most often by the anterior inferior cerebellar artery (4–7). Ephaptic transmission, or false crosstalk, subsequently occurs between axons of the facial nerve fibers (8–11). Because microvascular decompression abolishes the facial spasms in 80–90% of cases of HFS, one might conclude that vascular compression of the facial nerve is the root cause of HFS (6,7).

However, Aoki and Nagao (12) reported a case of HFS that improved immediately after posterior fossa exploration even though no vascular contact or other abnormality was identified at surgery. More importantly, neuroanatomical examination of 50 cerebellopontine angles has shown vascular loops compressing the facial and vestibulocochlear nerves in all cases, yet none of these patients had HFS (13). This would indicate that vascular compression alone is not sufficient to cause HFS. Other factors must be present before HFS occurs.

There are many similarities between HFS and benign essential blepharospasm (BEB), which is considered to be a disorder of the basal ganglia. Both BEB and HFS are debilitating disorders characterized by progressive involuntary spasms of the facial and neck muscles (14,15). These focal dystonias often begin as infrequent twitches or fasciculations of the orbicularis oculi muscles with subsequent spread to the lower face, jaw, and neck. Most cases have their onset in the sixth and seventh decades, being rarely observed at a younger age. Both disorders have a 60%–70% female preponderance and the two conditions may coexist in the same patient (14,16–19).

These similarities suggest that BEB and HFS represent entities with a common pathogenesis, although HFS is unilateral and BEB is bilateral. Consequently, in the following study we have grouped these two conditions.
The inciting cause of BEB and HFS is uncertain. We have encountered patients with BEB and HFS who had sustained major life stressors, involving the loss of a close relative or termination of a close relationship, shortly before the onset of the BEB or HFS. Major life stressors can lead to complicated grief or depression. Complicated grief, which has only recently been described, occurs in approximately 10%-20% of individuals who have experienced the loss of a loved one (20-24). We hypothesized that major life stressors and the development of complicated grief or depression might play a role in the pathogenesis of BEB and HFS. Accordingly, in the current case-control study we assessed the frequency of major life stressors and the prevalence of complicated grief and depression among subjects with BEB and HFS compared with control subjects.

METHODS

The study was approved by the institutional review board (IRB). Participants with BEB and HFS had been evaluated by one of the authors (L.N.J.) in the Neuro-Ophthalmology Clinic during the past 15 years. Control subjects consisted of individuals who had been evaluated by one of the authors (L.N.J.) during the past 2 months in the General Ophthalmology Clinic for refraction (eyeglasses) and were of approximately the same age as the participants with BEB/HFS. Potential participants were initially contacted by telephone. They were told the purpose of the study and that we would administer a questionnaire regarding their emotional state, in particular, how having lost people close to them or having ended close personal relationships affected them. They were also told that we wished to monitor changes in their mood and body temperature over a 14-week period (the latter components being the subject of another report). Written informed consent was obtained from study participants in accordance with the IRB.

Of the 106 potential participants (49 with BEB, 21 with HFS, and 36 control subjects) contacted by telephone, 46 subjects (16 with BEB, 7 with HFS, and 23 control subjects) were recruited to participate in the study. Almost all subjects who participated in the study lived within 25 miles of the medical center. Nearly all subjects who did not participate in the study lived more than 75 miles away from the medical center. Subjects who did not participate indicated that transportation to the medical center for refraction was the inciting cause of BEB and HFS, involving the loss of a close relative or termination of a close relationship, shortly before the onset of the BEB or HFS. Major life stressors can lead to complicated grief or depression. Complicated grief, which has only recently been described, occurs in approximately 10%-20% of individuals who have experienced the loss of a loved one (20-24). We hypothesized that major life stressors and the development of complicated grief or depression might play a role in the pathogenesis of BEB and HFS. Accordingly, in the current case-control study we assessed the frequency of major life stressors and the prevalence of complicated grief and depression among subjects with BEB and HFS compared with control subjects.

Study participants completed a questionnaire consisting of baseline demographic information including age, gender, marital status, health status, and mood. Participants then completed the Beck Depression Inventory-II (BDI-II) and the Inventory of Complicated Grief (25). Because the Inventory of Complicated Grief was originally developed to assess grief related to bereavement, we modified the Inventory of Complicated Grief to account for grief related to the loss of a close relationship as in "I feel myself longing for the person who died (or the relationship that ended)" (25). Participants subsequently underwent a structured interview in which they were queried as to major stressful life events that they felt had caused significant personal distress, in particular, the death of a loved one or ending of a close relationship (26). The approximate month and year that these major life stressors occurred were recorded so that the time interval between two major stressful events could be computed. A BDI-II score of 10 or greater was defined as being associated with depression (10–18 mild depression; 19–29 moderate depression; 30–63 severe depression), whereas a score less than 10 indicated an absence of depression. An Inventory of Complicated Grief score greater than 25 was defined as being associated with complicated grief, whereas a score less than 25 indicated an absence of complicated grief (25). Participants found to have complicated grief or depression or for whom questions provoked disturbing thoughts or feelings were referred for psychological counseling if they were not already under the care of a mental health specialist.

Statistical analyses were performed using SAS (version 9.1; SAS Institute, Inc., Cary, NC). Proportions are given for qualitative or categorical variables such as gender, marital status, and depression. When the control group and the BEB/HFS group are compared relative to quantitative variables that are approximately normal, two-sample t-tests were used. For distributions that were skewed or strictly ordinal, Wilcoxon rank-sum tests were used. For qualitative or categorical variables, \( \chi^2 \) tests were used. When variables related to the number of stressful life events are considered, it is logical to assume that the number could depend on the age of the subject. Consequently, when groups are compared relative to stressful life events, Cochran-Mantel-Haenszel (CMH) methodologies were used to allow for stratification by age group. Similarly, the shortest time between two stressful life events will depend on the total number of stressful life events experienced by an individual (the interval will most likely be shorter if there are more stressful life events within a specified time period). Three participants had reported only one stressful life event before the onset of BEB. The values for these participants were considered censored as of the time of onset of BEB. Analysis for shortest time between major lifetime stressors was done using a Cox
proportional hazards model with total number of stressful life events as a covariate. Because multiple tests were performed, an adjustment in the significance level was implemented using the false discovery rate (FDR) at a 0.05 level (27). Controlling the FDR is less conservative than using a Bonferroni adjustment for multiple tests. For the set of tests using the FDR, FDRs (denoted by \( P_{FDR} \)) are reported rather than the raw \( P \) values.

## RESULTS

The mean elapsed time from diagnosis of the facial spasm for the 23 participants with BEB/HFS was 8.7 ± 5.7 years (median 7.2; range 1.8–23 years). All participants with BEB/HFS had been treated with botulinum toxin injections over the years. There was no significant difference in gender distribution for the 23 participants with BEB/HFS (18 women and 5 men) compared with the 23 control subjects (13 women and 10 men). The mean age of the participants with BEB/HFS was 69.4 ± 11 years (median 72; range 43–84 years), and the mean age of control subjects was 69.0 ± 9 years (median 71; range 53–84 years). As expected, there was no significant difference in the mean ages of participants with BEB/HFS and control subjects (Table 1).

Thirteen (57%) of the 23 participants with BEB/HFS (8 with BEB and 5 with HFS) and 11 (48%) of the 23 control subjects scored in the depression range on the BDI-II. Of these 13 participants with BEB/HFS, 8 (62%) scored in the mild depression range (4 with BEB and 4 with HFS), 3 (23%) in the moderate depression range (2 with BEB and 1 with HFS), and 2 (15%) in the severe depression range (2 with BEB). Of the 11 control subjects, 9 (82%) scored in the mild depression range, 1 (9%) in the moderate depression range, and 1 (9%) in the severe depression range. Four (17%) of the 23 participants with BEB/HFS (2 with BEB and 2 with HFS) had complicated grief on the Inventory of Complicated Grief; all four also had scores indicative of depression on the BDI-II. Four (17%) of the 23 control subjects had complicated grief on the Inventory of Complicated Grief; 1 of the 4 control subjects with complicated grief did not have concomitant depression on the BDI-II. Seven (54%) of the 13 participants with BEB/HFS (3 with BEB and 4 with HFS) and 6 (55%) of the 11 control subjects with scores suggestive of depression on the BDI-II (which included one control individual with concurrent complicated grief) were unaware of their depression or complicated grief. The 7 participants with BEB/HFS and 6 control subjects had depressive symptoms with scores in the mild depression range on the BDI-II. These latter 13 individuals were offered a referral for appropriate therapy. There was no difference in the rate of depression (\( P_{FDR} = 0.717 \)) or complicated grief (\( P_{FDR} = 1.00 \)) between participants with BEB/HFS and control subjects. The odds ratios (ORs) (odds of outcome for participants with BEB/HFS relative to odds for controls) and 95% confidence interval (CI) for the OR were 1.42 (95% CI: 0.44, 4.53) and 1.00 (95% CI: 0.22, 4.59) for depression and complicated grief, respectively.

All 46 participants reported having had at least one major lifetime stressor that caused significant personal distress. Among the stressors were death of a loved one, divorce, serious marital problems and infidelity in a relationship, serious illness or injury, serious difficulties at work, fire destruction of a home, and profound financial loss. The mean number of total stressful life events for participants with BEB/HFS was 4.4 ± 1.9 events (median 4; range 2–11 events) and for control subjects was 4.1 ± 1.6 events (median 4; range 2–7 events). There was no significant difference in the total stressful lifetime events between participants with BEB/HFS and control subjects (\( P_{FDR} = 0.68 \)). Participants with BEB/HFS on average had 3.3 ± 1.5 major stressful life events (median 3; range 1–7 events) before the onset of the facial spasms. Facial spasms began within 1 year of a major stressful life event for 16 (70%) of the 23 participants with BEB/HFS. There were 3 participants with BEB who reported only 1 stressful life event before the development of facial spasms (although all 3 participants with BEB had at least 2 total stressful life events). Subsequent analyses below regarding the shortest time interval between stressful life events treat the values as censored as of the date of onset of the facial spasms.

The shortest time interval between two stressful life events was identified for each subject. This time interval was significantly shorter (\( P = 0.0048 \), Cox proportional hazards model with number of stressful life events as a covariate) for participants with BEB/HFS (median 0.3 years) than for control subjects (median 3.0 years). Eighteen (90%) of 20 participants with BEB/HFS had had two major stressful life events separated by 1 year or less. In contrast, only 7 (30%) of 23 control subjects had had two stressful life events separated by 1 year or less. The proportion of participants who had suffered two stressful life events separated by 1 year or less was significantly greater (\( P = 0.0007 \)) for participants with BEB/HFS than for control subjects. Nine (50%) of the 18 participants with BEB/HFS with two stressful life events separated by 1 year or less developed BEB/HFS within 1 year of experiencing the double stressful life event.

## DISCUSSION

We found a significant relationship between the interval between major life stressors and the development of BEB and HFS. Both types of facial spasms began within 1 year of a major stressful life event in 70% of cases.

These results corroborate the findings of Diamond et al (28) in which more than 90% of the female participants reported the onset or exacerbation of BEB.
TABLE 1. Features of the 23 participants with benign essential blepharospasm (BEB) and hemifacial spasm (HFS) and 23 control subjects

<table>
<thead>
<tr>
<th></th>
<th>BEB (n = 16)</th>
<th>HFS (n = 7)</th>
<th>Combined BEB/HFS (n = 23)</th>
<th>Control subjects (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women/Men</td>
<td>12:4</td>
<td>6:1</td>
<td>18:5</td>
<td>13:10</td>
</tr>
<tr>
<td>Age (mean ± SD; median; range)</td>
<td>69.3 ± 11.5; 72.5; 43–84 years</td>
<td>69.7 ± 9; 71; 53–83 years</td>
<td>69.4 ± 11; 72; 43–84 years</td>
<td>69.0 ± 9; 71; 53–84 years</td>
</tr>
<tr>
<td>Elapsed time from diagnosis (mean ± SD; median; range)</td>
<td>9.4 ± 6; 8.3; 1.8–23 years</td>
<td>7.0 ± 4.3; 4.1; 2.4–14 years</td>
<td>8.7 ± 5.7; 7.2; 1.8–23 years</td>
<td>—</td>
</tr>
<tr>
<td>Depression</td>
<td>8 (50%)</td>
<td>5 (71%)</td>
<td>13 (57%)</td>
<td>11 (48%)</td>
</tr>
<tr>
<td>Mild</td>
<td>50% (4/8)</td>
<td>80% (4/5)</td>
<td>62% (8/13)</td>
<td>82% (9/11)</td>
</tr>
<tr>
<td>Moderate</td>
<td>25% (2/4)</td>
<td>20% (1/5)</td>
<td>23% (3/13)</td>
<td>9% (1/11)</td>
</tr>
<tr>
<td>Marked</td>
<td>25% (2/4)</td>
<td>0</td>
<td>15% (2/13)</td>
<td>9% (1/11)</td>
</tr>
<tr>
<td>Complicated grief</td>
<td>2 (13%)</td>
<td>2 (29%)</td>
<td>4 (17%)</td>
<td>4 (17%)</td>
</tr>
<tr>
<td>Total major stressful life events (mean ± SD; median; range)</td>
<td>4.4 ± 2.1; 4; 2–11 events</td>
<td>4.1 ± 1.1; 4; 3–6 events</td>
<td>4.4 ± 1.9; 4; 2–11 events</td>
<td>4.1 ± 1.6; 4; 2–7 events</td>
</tr>
<tr>
<td>Proportion of facial spasms beginning within 1 year of a major stressful life event</td>
<td>11 (69%)</td>
<td>5 (71%)</td>
<td>16 (70%)</td>
<td>—</td>
</tr>
<tr>
<td>Shortest time interval between 2 stressful life events (median)</td>
<td>0.3 year</td>
<td>0.3 year</td>
<td>0.3 year</td>
<td>3.0 years</td>
</tr>
<tr>
<td>Proportion with 2 major stressful life events separated by 1 year or less</td>
<td>10 (80%) of 13</td>
<td>7 (100%) of 7</td>
<td>18 (90%) of 20</td>
<td>7 (30%) of 23</td>
</tr>
</tbody>
</table>

*Significant difference observed between cases and controls.

within 2 years of a dramatic life change, principally involving the death of a loved one or a divorce. More strikingly, our study documented that participants with BEB/HFS had a significantly shorter time interval between two stressful life events than did control subjects. For participants with BEB/HFS, the shortest time interval had a median value of 0.3 year (approximately 4 months) whereas for control subjects it was 3.0 years. Our study also documented that 90% of 20 participants with BEB/HFS had suffered two major stressful life events separated by less than 1 year and that 50% of the facial spasms began within 1 year of these stressful life events. Double stressful life events were less common among control subjects. These findings may explain why BEB and HFS are rarely encountered at a young age, as it is unusual for individuals to experience multiple stressful events so early in life (29,30).

We did not find the rate of complicated grief or depression among participants with BEB/HFS to be different from that of control subjects. However, our study was conducted, on average, 9 years after the onset of BEB and HFS. The number of individuals with complicated grief or depression might have been higher at the onset of BEB and HFS, but no different from the number of control subjects when tested 9 years later. Recent advances in the understanding of grief and depression have identified that a major life stressor is the most significant risk factor for depression and is the sine qua non of complicated grief (20,29–36).

It is estimated that a major life stress precipitates the onset of depression in 70% of individuals without a prior history of depression and that 20% of major life stresses will result in an episode of depression (31). Through kindling, major life stressors can initiate autonomous episodes...
of recurrent depression (31–35). Kindling results in upregulation of gene transcription factors leading to neurochemical alterations of inhibitory and excitatory neurotransmitters and sprouting and retraction of nerve terminals (31,32,35,37). Grief, when triggered by a major stressful life event, such as the loss of or separation from a loved one, may last several months.

We suspect that having a second major stressful life event, before or shortly after the resolution of grief from a prior major stressful event, may potentiate kindling mechanisms leading to BEB and HFS (33,34,38). This could occur through the activation and inhibition of brain centers, particularly in the basal ganglia, known to modulate blink reflex and mimetic facial movement (39–41).

A limitation of our study is that only 46 (43%) of 106 potential subjects participated after receiving the telephone inquiry. This could result in participant bias such that those choosing to participate did so because they believed that they had experienced either more or less stressful life events than had other individuals. However, the number of major stressful life events for both participants with BEB/HFS and control subjects was similar between the two groups and comparable with that for other studies (31–34). Most importantly, participants with BEB/HFS and control subjects were unaware that we had planned to assess the rate of two stressful life events separated by less than 1 year, which occurred significantly greater (P = 0.0007) for participants with BEB/HFS than for control subjects.

Another limitation of our study is that we relied on subjects recalling major stressful life events from the past. Recall bias could have affected the study outcome with regard to the number of events reported. Simon et al (42) have noted that recall errors more often involve underestimation of past morbidity than reporting or exaggerating episodes that did not actually occur. However, possible differences in the rate of recall would probably have been reduced because both groups were similar demographically, and the rates of depression and complicated grief were similar. Additionally, both groups had undergone similar structured interviews in which they were queried as to major stressful life events that caused significant personal distress. The striking difference between participants with BEB/HFS and control subjects with regard to the shortest time interval between two major stressful life events (median of 4 months for participants with BEB/HFS compared with median of 3 years for control subjects) suggests that recall bias most likely did not influence the outcome.

Finally, the modest number of participants in our study could falsely lead us to accept a relationship between closely spaced stressful life events and the development of BEB and HFS. A prospectively designed study recruiting subjects with recent onset of major stressful life events would eliminate the potential bias of a retrospective case-control study.

The findings in our study agree with those of Diamond et al (28) suggesting that closely spaced major stressful life events contribute to the development of BEB and HFS. The development of these focal dystonias was significantly related to the number of stressful life events within the preceding 1 year rather than to the total number of stressful life events.

ADDENDUM

A follow-up evaluation of one of the seven control subjects who had two closely spaced (within 1 year) stressful life events, but who did not have BEB or HFS at the time of the study, indicated that this subject has now developed BEB 1 year after experiencing the second stressful life event.

REFERENCES


Endovascular Treatment of a Bilateral Ophthalmic-Ethmoidal Artery Dural Arteriovenous Fistula

Vasilios Katsaridis, MD, PhD, Chrysanthi Papagiannaki, MD, and Constantinos Violaris, MD

Abstract: A 76-year-old man developed blurred vision, and cerebral angiography disclosed an anterior skull base dural arteriovenous fistula (DAVF) supplied by both ethmoidal branches of the ophthalmic arteries and draining through a single cortical vein. Selective catheterization of both ophthalmic arteries distal to the origin of the central retinal arteries and occlusion the fistula feeders with injections of n-butyl cyanoacrylate glue led to complete occlusion of the fistula with preservation of retinal perfusion. The visual symptoms are attributed to impaired retinal perfusion as the result of a steal phenomenon. With care, a DAVF in this location can be successfully treated endovascularly while preserving retinal perfusion by embolizing the ophthalmic artery distal to the origin of the central retinal arteries and avoiding any backflow of embolizing material.

CASE REPORT

A 76-year-old man was admitted to our hospital after an episode of loss of consciousness that had lasted a few minutes. Upon admission he was mildly disoriented and complained of headache. His family informed us that during the last month he had been complaining of blurred vision in both eyes but had not consulted an ophthalmologist.

Brain CT scanning showed a small ICH in the cortex of the left frontal lobe not requiring urgent surgical evacuation. MRA revealed a dilated and tortuous vascular structure coursing over the left frontal parasagittal cortex, raising the suspicion of a vascular malformation. Digital subtraction angiography (DSA) disclosed a high-flow DAVF supplied by both anterior ethmoidal arteries arising from both ophthalmic arteries. The DAVF was supplied by a single feeder from the right ethmoidal artery (Fig. 1A) and by multiple feeders from the left ethmoidal artery (Fig. 1B). The draining vein exhibited an aneurysmal dilatation at its proximal part, coursed tortuously, and drained to the superior sagittal sinus.

We proceeded to embolize the DAVF. Initially, we placed a guiding catheter in the petrous segment of the right internal carotid (ICA) and catheterized the right ophthalmic artery (OA). We navigated the tip of a Marathon microcatheter (Micro Therapeutics Inc., Irvine, CA) distal to the origin of the central retinal artery (CRA) and proximally to the origin of the ethmoidal artery (EA). Ultraselective angiography confirmed the correct position of the microcatheter tip with no opacification of the retina. We proceeded to occlude the segment of the OA that supplied the feeder of the DAVF with a very limited injection (0.1 mL) of a 15% mixture of n-butyl cyanoacrylate (NBCA) glue (Histoacryl; B. Braun, Melsungen, Germany) diluted in lipiodol/Ethiodol (Guerbet, Roissy, France). Immediate postinjection angiography showed no visualization of the DAVF and normal perfusion of the retina (Fig. 2).

Dural arteriovenous fistulas (DAVFs) account for 10%–15% of intracranial arteriovenous malformations (1). They are commonly classified according to the pattern of venous drainage by the systems of Cognard et al (2) and Borden et al (3). DAVFs rank higher (higher risk of rupture) if they drain through leptomeningeal or cortical venous branches. The system of Cognard et al (2) also includes the criterion of venous ectasia, which further increases the risk of rupture.

DAVFs of the ophthalmic-ethmoidal artery are rare. We present a case of a bilateral ophthalmic-ethmoidal artery DAVF that had caused an intracerebral hematoma (ICH) and presented challenges in endovascular management.
FIG. 1. A. Digital subtraction angiography (DSA) of the right internal carotid artery (ICA), lateral projection. It demonstrates a dural arteriovenous fistula (DAVF, arrow) supplied by the anterior ethmoidal branch of the right ophthalmic artery with drainage through a cortical vein that is aneurysmally dilated in its proximal portion. B. DSA of the left ICA, lateral projection. It demonstrates that the DAVF is also supplied by the anterior ethmoidal branch of the left ophthalmic artery with drainage through the same aneurysmally dilated cortical vein (arrow).

We then placed the guiding catheter in the left ICA and attempted to perform the same procedure on the left side. Despite using different combinations of microcatheters and guidewires, catheterization of the left OA proved impossible because of the reverse catheterization angle. We placed a second guiding catheter in the left vertebral artery and, under road mapping from both guiding catheters, we managed to catheterize the left OA, navigating the microcatheter through the basilar, left posterior cerebral, left posterior communicating, and left ICAs. The catheterization of the OA was achieved with little effort because the trajectory of the microcatheter in the posterior communicating, internal carotid, and the ophthalmic arteries was almost in a straight line (Fig. 3). After navigation of the

FIG. 2. Postembolization digital subtraction angiography of the right internal carotid artery, lateral projection, early arterial phase. The dural arteriovenous fistula is no longer visualized.

FIG. 3. Unsubtracted angiography of the left internal carotid artery, lateral view. The ophthalmic artery has been selectively catheterized through a second guiding catheter in the left vertebral artery following a course through the basilar, left posterior cerebral, left posterior communicating, and left internal carotid arteries.
microcatheter tip in the OA distal to the origin of the central retinal artery, we occluded the multiple DAVF feeders with an injection of 0.4 mL of a 10% mixture of NBCA glue in lipiodol/Ethiodol that reached the beginning of the draining vein. The final postembolization DSA of the left ICA showed complete occlusion of the DAVF with no visualization of the draining vein but normal perfusion of the retina of the left eye (Fig. 4).

The patient was extubated immediately postoperatively and was discharged 5 days later in excellent condition, claiming that he no longer experienced blurring of vision. CT angiography 6 months later showed no evidence of flow in the DAVF. The patient reported completely normal vision with a best-corrected visual acuity of 20/20 in both eyes and no abnormalities on ophthalmoscopy.

DISCUSSION

DAVFs are abnormal shunts within the dura. They are mostly idiopathic in origin, although trauma, infection, and hormonal disturbances have been implicated as etiologic factors. They are usually supplied by meningeal branches but are also supplied from cutaneous or osseous ones. They most frequently drain into venous sinuses; cortical drainage is very rare (4). The pattern of cortical venous drainage seen in our patient carries a substantially higher risk of rupture and intracranial bleeding, warranting more aggressive treatment (4,5).

DAVFs of the anterior cranial fossa almost constantly drain through cortical veins. Arterial supply arises from the anterior meningeal artery when the fistula is located laterally and from the anterior and posterior EAs when it is located by the midline (4). The DAVF of our patient was located in the anterior cranial fossa near the midline and posterior to the left frontal sinus. It was supplied by both anterior EAs, branching from the OAs, with the right one crossing the midline. The DAVF was drained exclusively by a left frontal cortical vein that exhibited an aneurysmal dilatation (ectasia) at its proximal part.

The investigation of such lesions includes CT and MRI as well as MRA, but the definitive diagnosis is made with DSA. A novel method of discovery of DAFVs of the anterior skull base was described by Fiori et al (6) with the use of pulse-wave Doppler.

The draining vein in our patient had ruptured and caused an ICH. A similar case of DAVF supplied by both EAs was described by Tiyaworabun et al (7) with the difference that the drainage was through a cerebral vein into the vein of Rosenthal and the straight sinus. It is interesting that the proximal part of the draining vein exhibited an aneurysmal dilatation exactly as in our patient and had also caused an ICH. Unlike our patient, the patient of Tiyaworabun et al (7) was treated surgically (and with success).

Two other cases of DAVFs of the anterior cranial fossa supplied by the anterior and posterior EAs have been reported by Ito et al (8), differing from our patient in that they had additional arterial supply from the external carotid system. The draining vein had an aneurysmal dilatation in those patients as well.

Our patient had been complaining of blurred vision during the month before the rupture of the DAVF. This could be attributed to a steal phenomenon from both central retinal arteries. Steal phenomena are common in DAVFs and can cause a variety of symptoms such as cranial nerve palsies because most cranial nerves are supplied by meningeal arteries (4). Xiong et al (9) reported a case of monocular amaurosis fugax due to a DAVF of the falcine artery originating from the OA and attributed the symptomatology to a steal phenomenon.

The endovascular treatment we attempted resulted in resolution of the fistulous communication while preserving the supply to both retinas. The improvement in the patient's vision can be attributed to increased perfusion of the retinas due to the cessation of the steal phenomenon. In a series of vascular lesions involving the OA, Lefkowitz et al (10) reported the successful embolization of four DAVFs of the anterior cranial fossa with preservation of vision. In that series, the authors relied on Amytal testing to assess the safety of the point of injection of embolic material. We did not perform an Amytal test and relied solely on angiographic findings. We injected the NBCA mixture only when we were certain that the microcatheter tip was distal to the origin of the central retinal artery, and the retina was not opacified by contrast injections from that point.

![FIG. 4. Postembolization digital subtraction angiography of the left ICA, lateral projection, early arterial phase. The DAVF is no longer visualized.](image-url)
The integrity of the central retinal artery was achieved by slow and careful injection of the material, not allowing it to backflow into the OA.

An alternative to endovascular treatment of this DAVF would have been surgical coagulation and disconnection of the fistula, a straightforward, well-proven, and established form of therapy. Surgical treatment of DAVFs has yielded excellent results but can be tedious, with the risk of morbidity from blood loss due to injury to fragile and engorged vessels in the adjacent brain (11). Furthermore, craniotomy has inherent risks of infection and postoperative hemorrhage and constitutes major discomfort for the patient compared with endovascular embolization. Intra-arterial embolization of this particular DAVF had a significant risk of central retinal artery occlusion by embolic backflow or ophthalmic artery injury during the microcatheterization. Our experience with the use of liquid embolic agents influenced our decision to perform endovascular embolization of the lesion. The risk of compromise of the blood supply to the retina was constantly evaluated during the intervention, and we were ready to abort the endovascular treatment if it was considered dangerous. Fortunately we were able to embolize the DAVF and preserve the blood supply to both retinas.

REFERENCES
Posterior Ischemic Optic Neuropathy After Minimally Invasive Prostatectomy

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Abstract: Two patients developed postoperative ischemic optic neuropathy (ION) after laparoscopic radical prostatectomy. One operation was robotically assisted; the other was performed with the conventional laparoscopic technique. These new minimally invasive techniques offer many advantages, but they require steep supine head-flexed (Trendelenburg) positioning. Until they are mastered by surgeons, operative times may be prolonged beyond those associated with the traditional technique. As a result, ION may occur more frequently.

Ischemic optic neuropathy (ION) is uncommon after prostate surgery for benign or malignant disease (1-3). Studies of perioperative ION have implicated prone positioning and significant blood loss as likely risk factors (4), neither of which typically occurs in modern open radical retropubic prostatectomy (RRP) or transurethral resection of the prostate (TURP). Laparoscopic radical prostatectomy (LRP) has been increasingly used since its introduction in 1997. Approximately 35,000 robot-assisted laparoscopic prostatectomies (RALPs) were performed in the United States in 2006. Some techniques use robotic technology for improved depth perception and eye-hand coordination. A skilled surgeon can complete the RALP procedure in approximately 150 minutes with minimal blood loss (5), but even an experienced urologic surgeon new to the procedure may need to perform more than 150 laparoscopic operations to become proficient in manipulating unfamiliar instruments and acclimated to a restricted field of view (6). During this transitional period, the procedure can be prolonged beyond the average time of 160 minutes for an open RRP, and blood loss may be increased. In addition, LRP and RALP require steep, supine, head-flexed (Trendelenburg) positioning (7), which may produce venous stasis or facial edema, increasing the risk of ION (8).

The following two cases illustrate how the added operative time and compromised patient positioning may be factors in inducing ION after RALP or LRP.

CASE REPORTS

Case 1

A 62-year-old man underwent RALP for adenocarcinoma of the prostate. General anesthesia was induced using intravenous propofol, lidocaine, and vecuronium and was maintained with desflurane. Results of preoperative laboratory studies performed 1 week before the procedure were all within normal ranges, with a hemoglobin of 14.2 g/dL. Blood pressure on the morning of surgery was 127/66 mm Hg, and the patient had no history of hypertension. Shortly after induction of anesthesia, the patient became hypotensive (90/45 mm Hg) for about 1 hour with a nadir of 85/35 mm Hg. No blood loss had occurred.

The patient was then placed into a steep Trendelenburg tilt in a low lithotomy position. The total operative time was 6 hours 35 minutes, and for >5 hours, the blood pressures were maintained in a range of 90–135 mm Hg systolic and 50–95 mm Hg diastolic. Multiple intraoperative hemoglobin measurements ranged from 8.2 to 11.9 g/dL. Approximately 4 hours into the procedure, after the patient had received 4,300 mL of lactated Ringer's solution and had lost approximately 550 mL of blood, the patient was given a transfusion of 1 unit of packed red blood cells. The procedure was prolonged by the loss of one needle during bladder repair but concluded uneventfully. Total blood loss was 1,200 mL.

On the first postoperative day, the patient complained of "purple vision" and loss of inferior visual fields in both eyes. His symptoms worsened when he was upright. On that day, a neuro-ophthalmologist recorded visual acuities...
Weber et al

FIG 1. Case 1. Humphrey visual fields, performed 1 day after prostatectomy, demonstrate bilateral inferior altitudinal defects.

of 20/25 in both eyes. He noted no facial edema. Optic discs were described as of normal appearance with a cup/disc ratio of 0.25. Automated Humphrey visual fields demonstrated bilateral inferior altitudinal defects (Fig. 1). Hemoglobin was 9.7 g/dL. Blood pressure and pulse were normal. The patient was observed for 3 days and discharged, during which time his vision remained unchanged.

At a follow-up examination 3 months later, visual acuities were 20/20 in both eyes, and visual field examination confirmed stable loss of bilateral inferior fields. Ophthalmoscopy disclosed bilateral superotemporal optic disc pallor (Fig. 2).

Case 2

A 64-year-old man underwent a laparoscopic prostatectomy without the assistance of robotic technology. General anesthesia was induced, and he was put in a steep Trendelenburg position shortly thereafter. Preoperatively hemoglobin was 11.4 g/dL, total cholesterol was 374 mg/dL, and low-density lipoprotein was 260 mg/dL. The only medication was olmesartan for hypertension. Blood pressure on the morning of surgery was 130/80 mm Hg, within his usual range.

Total operative time was approximately 9 hours, and blood pressure varied from 100/50 to 165/70 mm Hg. At no time was he made intentionally hypotensive. Total blood loss was 500 mL, and no transfusions were given. His procedure was considered otherwise uncomplicated. During the procedure, the patient received 6,500 mL of intravenous crystalloids. Hemoglobin had dropped to 9.3 g/dL on the first postoperative day.

When the patient awoke after surgery, he complained of seeing a rainbow in his superior fields that lasted for a few seconds but shortly thereafter he noted that “everything went black.” When the patient’s wife first saw him after surgery, there was so much facial swelling that she reported she could barely recognize his face.

On the following day, an ophthalmologist noted no light perception vision in both eyes and administered intravenous methylprednisolone, a treatment that was terminated after 1 day because of corticosteroid-induced psychosis. Brain MRI and MRA were normal.

Twelve days after surgery, a neuro-ophthalmologist recorded light perception vision in the right eye and no light perception vision in the left eye. The pupils did not constrict to direct light. The right optic disc had a 0.1 cup with mild temporal pallor; the left optic disc had a 0.2 cup with more notable temporal disc pallor. The remainder of the ophthalmologic examination was normal. Blood pressure was 178/92 mm Hg. Two months after surgery, the patient had had no improvement in vision and now had substantial optic disc pallor in both eyes.

DISCUSSION

When compared with standard RRP, RALP and LRP performed by experienced surgeons have been shown to reduce intraoperative blood loss and hasten postoperative recovery (5). The advantages of the robotic system include a stereoscopic view for depth perception, masking of an operator’s tremor by filtering hand movements, and more intuitive movement of the instruments themselves (5). The main disadvantage of the robotic system is added cost for the system and for each procedure. Another significant disadvantage is the total surgical time—either laparoscopic technique takes longer than conventional RRP to allow for equipment setup and testing.

In the two previously reported cases of ION after conventional RRP, prolonged, intentional hypotension was reported (1,3). Hemodilution of almost 50% was reported in the single case of vision loss after TURP (2). In our two cases, these factors were not so prominent. Rather, two other factors may have played a causative role: prolonged operative time and steep supine, head-flexed (Trendelenburg)
positioning. Case #2 had marked facial edema after a 9-hour procedure. Impaired venous return has been implicated in ION after radical neck dissection and jugular ligation (4).

Although our Case #1 lost vision inferiorly, he fortunately retained good foveal function with 20/20 vision in each eye. Our Case #2 underwent a longer procedure and had significant facial swelling and a more devastating visual outcome. LRP, especially when performed by an experienced surgeon with the da Vinci surgical robot, may reduce surgical morbidity and postoperative functional recovery. At this time, such technology is found primarily at teaching centers where the cost of the robot can be justified for research and training but also where a large percentage of RALPs are done by resident physicians and more experienced surgeons who are nevertheless naïve to the robotic procedure. The result may be longer than average surgical times and prolonged positioning of the patient in a less favorable position. Therefore, ION may become more frequent as laparoscopic techniques are more widely used.

REFERENCES
Bilateral Macular Retinitis as the Presenting Feature of Subacute Sclerosing Panencephalitis

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Abstract: Two patients presented with retinitis as the initial clinical manifestation of subacute sclerosing panencephalitis (SSPE), a delayed neurologic complication of measles. In one patient, the ocular involvement preceded the neurologic symptoms by 4 weeks and in the other patient by 4 years. The diagnosis of SSPE was suspected when neuropsychiatric manifestations appeared and was confirmed by the typical panencephalitic electroencephalography changes, neuroimaging features of panencephalitis, and high titers of measles antibodies in serum and cerebrospinal fluid. Although SSPE is an untreatable illness, recognition of this unusual presentation is valuable to allow earlier diagnosis and institution of palliative measures.

SUBJECTIVE

Subacute sclerosing panencephalitis (SSPE) is a progressive inflammatory disease of the central nervous system caused by a persistent aberrant measles virus infection. The annual incidence rate varies from 1 to 4 per million in developed countries (1). However, in developing countries the incidence is higher because a larger proportion of the total population is younger than 2 years of age (2). In India, the annual incidence rate is reported to be as high as 21 per million (1,2). Ocular manifestations of SSPE include optic neuritis (3), viral retinitis (4), choriororetinitis (5–8), and cortical blindness (9,10). We report two patients with SSPE who initially presented with visual loss.

CASE REPORTS

Case 1

A 20-year-old man presented with sudden painless loss of vision in both eyes of 20 days’ duration. The vision in the right eye had worsened rapidly over the previous 2 weeks. His general health was normal. He had had measles at the age of 9 months.

He appeared well nourished and was cooperative and alert. He was afebrile. General physical examination was completely normal. Best-corrected visual acuities were 20/400 in right eye and 20/30 in left eye. Ophthalmoscopy (Fig. 1) showed bilateral macular gray-white retinal lesions with geographic borders and yellow exudates at their edges and bilateral temporal pallor of the optic discs. There was no vitreous inflammation. There were no other ophthalmic abnormalities and the neurologic examination, including mental status, was normal.

Fourteen days later, he developed insomnia and psychotic behavior. He was seen by a psychiatrist and was given antipsychotic medications. He subsequently developed tremor of the upper extremities and paresis of the left lower extremity.

The white blood cell count was 7,100/mm³, hemoglobin was 14 g/dL, and erythrocyte sedimentation rate (ESR) was 22 mm/h. Results of anti-streptolysin titers and smears for malarial parasites were negative. Blood glucose, electrolytes, liver and renal panels, thyroid-stimulating hormone, anti-double-stranded DNA antibody, anti-nuclear antibody, blood and urine culture, chest X-ray, echocardiography, and abdominal ultrasound were normal. Cerebrospinal fluid showed 5 cells/mm³ (all lymphocytes), 32 mg/mL protein, and 61 mg/dL glucose and negative results for Gram and acid-fast stains and polymerase chain reaction (PCR) for herpes simplex virus (HSV) and Mycobacterium tuberculosis. Results of arbovirus serology were negative.

Electroencephalography (EEG) showed a disorganized pattern with low-amplitude random dysrhythmic slowing and predominant delta and theta waves. Alpha waves of 9–10 Hz were intermixed with low-voltage slow waves. Periodic high-voltage slow waves in the delta range were also seen with a right-sided focus and no abnormal sharp waves or spikes. These findings were interpreted as showing a generalized encephalopathy. Brain MRI showed high T2 signal abnormalities in the basal ganglia (not shown).

Serum anti-measles IgG antibody was elevated at 16.59 enzyme immunoassay (EIA) units (normal < 10) and...
IgM (1.02 EIA units) (normal < 1.0) was normal. CSF anti-measles IgG antibody was 8.5 EIA units (normal < 1.0) and IgM was normal.

A diagnosis of SSPE was made. The patient was treated with sedatives and antiepileptic drugs but became quadriplegic and aphasic and died within 3 months.

**Case 2**

A 25-year-old man presented with decreased vision in both eyes over 20 days. He had been examined 3 years earlier at our hospital with similar complaints and bilateral viral retinitis had been diagnosed. On that occasion, his best-corrected visual acuity was 20/60 in the right eye and 20/400 in the left eye. He reported no decline in vision from 4 years ago until 20 days earlier. He had had measles infection at age 7. Otherwise he was healthy.

He was afebrile, and general and neurologic examinations were normal. Best-corrected visual acuity was 20/200 in the right eye and 20/800 in the left eye. Pupillary reactions were sluggish in both eyes. Anterior segment examination and the vitreous were normal. Fundus examination showed bilateral macular retinal pigment epithelial atrophy (Fig. 2). Within 10 days, the patient developed irritability and reduced attention. A few days later, he became increasingly withdrawn and emotionally labile. Later he developed intermittent, random, low-amplitude, lightning-like jerking movements of the extremities.

Blood count and ESR were normal, and blood herpes simplex viral titers were elevated. Serum anti-measles IgG antibody was elevated at 18.20 EIA units (normal <10) and IgM was negative (normal < 1). CSF anti-measles IgG antibody was 22.5 EIA units (normal < 10) and IgM was normal. EEG showed an encephalitic pattern (Fig. 3). T2 brain MRI showed a hyperintense signal in the gray matter with loss of gray-white definition and obliteration of sulci of the parieto-occipital lobe (Fig. 4).

He was initially treated for a diagnosis of herpes encephalitis with 1,500 mg/day intravenous acyclovir in divided doses for 1 week and transferred to a tertiary neurocenter, where the repeat CSF anti-measles antibody titer was found to be 1:625 and anti HSV IgG antibody was 1:25 (HSV-1 IgG levels: negative 0.90, equivocal 0.91–0.99, and positive > 1.0). SSPE with atypical features was diagnosed, and the patient was treated with antiseizure medications, inosiplex, and interferons. He was followed for 6 months with no clinical improvement and was lost to follow up.
FIG. 3. Case 2. Electroencephalography shows a disorganized pattern with low-amplitude random dysrhythmic slowing and a periodic high-voltage slow wave in the delta range (periodic complexes) consistent with encephalitis.

FIG. 4. Case 2. T2 brain MRI shows hyperintense signal in the gray matter with loss of gray-white definition and obliteration of sulci of the parieto-occipital lobe consistent with panencephalitis.

DISCUSSION

The diagnosis of SSPE is based on clinical features, characteristic EEG changes, elevated CSF globulin levels (>20% of total protein), raised measles antibody titers in blood and CSF, and typical histopathologic findings on brain autopsy. The clinical features consist of personality and behavioral changes and worsening school performance, followed by myoclonic seizures, paresis, dyspraxias, memory impairment, language difficulties, blindness, and eventually obtundation, stupor, and coma (10).

Most patients give a history of having acquired measles before 2 years of age. The latent period between measles infection and SSPE is 6–8 years in most cases but may range from 3 months to 18 years. Once SSPE is identified, clinical progression is variable. Death usually occurs within 1–3 years after the onset of symptoms. Approximately 10% of patients have a fulminant course with death occurring within a few months after onset. Another 10% of patients survive for 4–10 years (1). Atypical presentations include isolated psychiatric manifestations, poorly controlled seizures, or isolated extrapyramidal syndromes such as chorea or hemiparkinsonism (11,12). A stroke-like onset has also been described (11).

A multitude of neuro-ophthalmic and retinal findings are associated with SSPE, and ocular involvement appears to occur in at least 50% of cases (3–9). The most characteristic lesion is a necrotizing retinitis (13). It usually manifests as a focal area of retinitis in the macula. Occasionally described as a chorioretinitis, it appears to preferentially affect the retina with secondary involvement of the retinal pigment epithelium and choroid. Most commonly, it appears as a ground-glass whitening of the retina with ill-defined margins and a mottling of the underlying pigment epithelium. Sometimes there may be a red-orange color change in the macular area (13). This process may progress to involve most of the posterior pole and peripheral retina. There may be associated retinal changes such as edema, hemorrhage, detachments, venous dilatation, vascular occlusions, and retinal pigment epithelial detachments. There is little or no vitreous inflammation or involvement of retinal vessels or satellite lesions. These features help in distinguishing SSPE from other inflammatory retinal disorders such as toxoplasmosis and Behçet disease.

In the cases reported by Takayama et al (14), blurred vision was the initial symptom in more than half (15,16). Basal ganglion involvement occurs on MRI in 20%–35% cases, as in our Case 1 (15,16).

Our cases are unusual in presenting with retinitis as the initial clinical manifestation of a rare condition. However, because developing countries have a very high prevalence of measles, SSPE should be kept in mind in patients with retinitis to avoid diagnostic errors and institute early specific management.

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Isolated Cortical Visual Loss With Subtle Brain MRI Abnormalities in a Case of Hypoxic-ischemic Encephalopathy

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Abstract: A 16-year-old boy who was briefly asystolic and hypotensive after a motor vehicle accident complained of abnormal vision after recovering consciousness. Visual acuity was normal, but visual fields were severely constricted without clear hemianopic features. The ophthalmic examination was otherwise normal. Brain MRI performed 11 days after the accident showed no pertinent abnormalities. At 6 months after the event, brain MRI demonstrated brain volume loss in the primary visual cortex and no other abnormalities. One year later, visual fields remained severely constricted; neurologic examination, including formal neuropsychometric testing, was normal. This case emphasizes the fact that hypoxic-ischemic encephalopathy (HIE) may cause enduring damage limited to primary visual cortex and that the MRI abnormalities may be subtle. These phenomena should be recognized in the management of patients with HIE.

CASE REPORT

A 16-year-old boy was an unrestrained driver of a car that collided with a tree at an unknown speed. Emergency rescue required 40 minutes to extricate him from the vehicle. He was unresponsive at the scene and was promptly intubated, after which he suffered a 5-minute period of asystole. Pulse and blood pressure were recovered with resuscitation, including the use of atropine and epinephrine. Upon arrival at our hospital, he was unresponsive. A bilateral pneumothorax, thigh burn, multiple rib fractures, and a T1 vertebral fracture were found. A head CT scan on the day of arrival was normal.

Upon extubation 5 days later, he was alert but disoriented to time and amnestic for the accident yet able to recall events preceding it. He immediately reported that he could not see. A bedside ophthalmologic examination disclosed that visual acuity was hand movements in both eyes. Pupillary examination was normal, extraocular movements were full on command, and he was orthophoria. Ophthalmoscopic examination was normal in both eyes. On the second day after extubation, results of bedside mental status testing were normal, and he could remember the accident.

Brain MRI performed 11 days after the accident ("first MRI") demonstrated mildly increased curvilinear T2/FLAIR signal along the lateral margins of the posterior portions of the lentiform nuclei on both sides, not associated with restricted diffusion (Fig. 1A–D). There was subtle high T2/FLAIR signal and restricted diffusion in the splenium of the corpus callosum. There were small foci of enhancement within the posterior parietal subcortical white matter and centrum semiovale attributed to shear injury, and a small focus of curvilinear gyral enhancement posteriorly at the right occipital pole (Fig. 1E–F) which was attributed to trauma. These findings did not provide an adequate explanation for the patient's poor vision.
FIG. 1. Brain MRI performed on day 11 after the accident ("first MRI"). Axial FLAIR (A), Fast spin echo (FSE) T2 (B), diffusion (C), and ADC map (D) at the level of the basal ganglia. Postcontrast sagittal image (E), and T1 coronal image (F). There is high FLAIR and T2 signal along the lateral aspects of the posterior lentiform nuclei (small arrow, A, B). There is minimally increased FLAIR signal in the medial occipital lobes, more on the right (large arrow, A). The diffusion image (C) and ADC map (D) are normal. There is focal cortical gyriform enhancement in the right occipital lobe (large arrow, E), and several punctuate foci of enhancement in the centrum semiovale and subcortical left parietal white matter (small arrows, E, F).

Three weeks after the accident, he was discharged with impaired mobility due to right acetabular and left ulnar fractures as well as a healing right thigh skin graft. Before discharge he had undergone formal psychometric testing that revealed tactile perceptual and spatial reasoning abilities within normal limits. Six weeks after the accident, repeat psychometric testing revealed normal attention and high average scores on memory and learning.

Twelve weeks after the accident, he reported that his vision was not normal. Ophthalmologic examination disclosed visual acuities of 20/20 in both eyes. The remainder of the examination was normal except for severely constricted Humphrey visual fields with mean deviations (MDs) of 26.8 dB for the right eye and 22.8 dB for the left eye without a hemianopic pattern (Fig. 2). Goldmann visual fields were also constricted without clear localizing features. He had no difficulty recognizing objects, familiar, or famous faces, counting objects in an array, localizing objects in space, or interpreting action photographs.

Twenty-four weeks after the accident, visual acuity was 20/15 in both eyes, but visual fields remained severely constricted with stable MDs of 28 dB for the right eye and 28 dB for the left eye with the same pattern as noted previously (Fig. 3). A repeat MRI performed 24 weeks after the accident ("second MRI") was reported as showing resolution of previously noted signal abnormalities and enhancement. Because of the persisting profound visual field defects,
Margolin et al

FIG. 2. Humphrey 24-2 visual fields performed 2 months after the episode of cardiogenic hypoxia and hypotension show markedly high thresholds in all quadrants without clear hemianopic features. Visual acuity was 20/15 in both eyes.

A review of the second MRI study was conducted. It was reinterpreted as showing volume loss of the medial occipital lobes, including the area of the primary visual cortex, without signal abnormalities on the FLAIR images (Fig. 4). The first MRI (Fig. 1) was also reviewed and reinterpreted as showing increased FLAIR signal in the occipital cortex. The subtle area of occipital gyriform enhancement was reinterpreted as indicating a subacute ischemic lesion.

FIG. 3. Visual fields performed 3 months after the episode of cardiogenic hypoxia and hypotension show little change relative to those of Fig. 2.

FIG. 4. Axial FLAIR MRI performed 6 months after the study in Fig. 1. It demonstrates loss of volume in the occipital lobes with prominent medial occipital sulci (arrows).

One year after the accident, visual acuity remained 20/15 in both eyes, and visual fields were slightly improved at MDs of 23 dB for the right eye and 17.8 dB for the left eye (Fig. 5). Goldmann visual fields showed enough breadth to permit legal driving in the state of Michigan.

DISCUSSION

Our patient is notable for having developed profound and persistent hypoxic-ischemic damage to the primary visual cortex without other enduring neurologic deficits. Recognition of this phenomenon was delayed because the visual field lacked the typical hemianopic features associated with visual cortical damage, and the MRI signs were so subtle—on the early and the late studies—as to be initially overlooked. We attribute that error in part to the fact that the primary visual cortex is not widely recognized as an isolated target in HIE.

If hypoxia is the main insult, the thalamus (including lateral geniculate body), hippocampus, globus pallidus, and deep cerebellar nuclei are described as experiencing the greatest damage (5). If hypoperfusion is the main insult, as in the cardiac arrest of our patient, damage is said to occur predominantly in the watershed areas (arterial border...
zones) (5,7,8). In adults, these regions include the cerebral and cerebellar cortex, the hippocampus, and the basal ganglia (1,7,9,10). In preterm infants, it is the periventricular white matter (11–14).

The posterior cerebral watershed zone involves the parieto-occipital region. Ischemia to this region produces the visual spatial and ocular motor deficits of the Balint-Holmes syndrome (9,15,16). In our patient, there were no features of this syndrome. In previous clinical descriptions of the visual consequences of HIE, homonymous hemianopia has been described, but always in combination with features of the Balint-Holmes syndrome (15).

The reported MRI abnormalities in adult HIE have been associated with the cerebral and cerebellar gray matter, particularly the large cell layers of the neocortex and Purkinje cells of the cerebellar cortex, along with the hippocampus, basal ganglia, and thalami (1–6,7,11,17). In the hyperacute period after the ischemic event (<24 hours after the insult), MRI signal abnormalities have been found on diffusion-weighted imaging (DWI) in the cerebellum, basal ganglia, and cerebral cortex (1,17). Later in the acute and the early subacute period (24 hours–14 days), abnormal signal is also demonstrable on the T2 and FLAIR sequences. In one report, changes on DWI were prominent in the white matter in the early subacute period, representing post-hypoxic demyelination (3). On T1 images, cerebral swelling and obscuration of gray-white matter differentiation has been described (4,17). Diffusion abnormalities after focal ischemia tend to peak at 2–3 days after the event and tend to fade by 10–12 days. Enhancement after contrast administration is often demonstrated in the subacute period and may persist for several weeks. In the late subacute period (14–20 days) and in the chronic period (>20 days), conventional MRI shows signs of laminar necrosis (1,2,18,19) and volume loss.

Our patient had no substantial MRI abnormalities 11 days after the HIE event and volume loss limited to the medial occipital region 6 months later. Only one previous report has described MRI changes in the visual cortex after hypoxic injury due to respiratory arrest after a motor vehicle accident (20). There was high T1 signal 1 month after the injury and high T2 signal in the same area 4 months after the accident. DWI was not performed. The patient reportedly had a bilateral visual disturbance that persisted on a 6-month follow-up. This disturbance was attributed to “cortical blindness” but not further delineated.

Interestingly, hypoglycemia in the neonate has also been reported to have a propensity for occipital distribution of MRI changes. Unlike the watershed pattern seen in neonatal HIE, neonatal hypoglycemia shows occipital MRI abnormalities in up to 82% of cases, with half of these infants sustaining visual impairment (21–25). In adult post-hypoglycemic coma, MRI changes variably involve the hippocampus, basal ganglia, and the cerebral cortex without mention of an occipital lobe predilection (26,27). Laminar necrosis is common pathologic finding (28) in these patients.

Although not traditionally acknowledged as a vulnerable region in HIE, the primary visual cortex has features that could make it susceptible to damage in this condition. It lies at a remote region of arterial blood supply, the terminus of the posterior cerebral artery. Under hypotensive conditions, perfusion may not be adequate. The dual arterial supply of the occipital tip from posterior and middle cerebral arteries may account for preservation of the central visual field, including visual acuity. The topographic role of the primary visual cortex precludes any reduplication of neurologic function. That is, each point in visual space is represented in only one tiny cortical region. In case of damage, ischemic or otherwise, there is no back-up.

REFERENCES

Room Tilt Illusion Influenced by Head Position

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Abstract: After a low brainstem stroke, a 73-year-old man experienced episodes of 90° tilting of the visual environment in the sagittal plane evoked or terminated by voluntarily changing his head position. The episodes ceased 10 days after the stroke. This provocation by head position supports the idea that pathologic visual-vestibular interaction is at the basis of the room tilt illusion.


Room tilt illusion is a perception characterized by transient 90° or 180° rotation of the visual surroundings (1). This phenomenon can occur in the frontal, sagittal, or horizontal planes and is usually associated with verteobasilar ischemia. This perceptual phenomenon may result from impairment of visuospatial inputs and their cortical integration (1,2). We are not aware of reports indicating whether and how it can be induced or stopped voluntarily. Herein we report a patient who, after a pontocerebellar ischemic event, experienced episodes of 90° tilting of the visual environment in the sagittal plane. The patient could control the occurrence of illusion by changing the position of his head.

CASE REPORT

A 73-year-old man with hypertension and atrial fibrillation experienced the sudden onset of dizziness accompanied by diplopia, ataxia, dysarthria, and bilateral hyperacusis. On the day of hospitalization, physical examination had shown saccadic pursuit, small rapid nystagmus on upgaze, and coarse nystagmus evoked by lateral gaze, as well as ataxia of speech, extremities (left more than right), and gait. Mental status was normal.

Neuro-ophthalmologic examination disclosed a best-corrected visual acuity of 20/25 in both eyes and normal visual fields. The patient displayed a slight head tilt to the left and a 2-degree right hypertropia in primary gaze position, upgaze, and downgaze. Subjective visual vertical measurements consistently showed a tilt to the left of 3-5 degrees with right eye fixating and 6-7 degrees with left eye fixating, as measured on the screen described by Safran et al (3). Left internuclear ophthalmoplegia and left Horner syndrome were also noted.

Brain MRI performed 1 day after hospitalization revealed ischemia in cerebellar and pontine areas in the territory of the left superior cerebellar artery (Fig. 1). Cerebral digital subtraction angiography demonstrated arterial stenoses at several levels, including the left vertebral artery at its junction with the basilar artery and in the initial part of the left superior cerebellar artery (Fig. 2). The ataxic manifestations regressed gradually.

From the 4th to the 10th day after the stroke, the patient described episodes of static misperception of the visual environment. The episodes occurred 3–4 times per day. During them, he would perceive the visual environment as suddenly tilted 90° backward in the sagittal plane. In his hospital bedroom, when looking at a bed positioned in front of him, he suddenly perceived it as turned vertically. The man lying in that bed now appeared upright, hanging in front of the bed and facing him directly. (The patient was so amazed by this distorted perception that he did not explore the rest of the room.) This illusion was instantaneous, static, and disappeared completely within approximately 30 seconds. The patient noted that he was able to induce or stop the perceptual phenomenon by changing the position of his head. Thus, he could provoke the illusion by extending his neck or lying horizontally in the bed. In contrast, the illusion disappeared immediately when he closed his eyes, tilted his head forward, and opened his eyes.

DISCUSSION

The first description of room tilt illusion appeared in 1805 when Bishopp (4) reported a complete upside-down visual inversion and considered it a manifestation of hysteria.
FIG. 1. Diffusion MRI shows restricted diffusion in the left cerebellum and pons, consistent with infarction in the domain of the left superior cerebellar artery (arrows).

Since then, most of the cases of transient misperception of visual surroundings have been reported in association with brainstem (1,5), cerebellar (6), cortical (7), or labyrinthine disorders (8). In our patient, there was clinical and imaging evidence of brain stem ischemia. Ophthalmic examination showed persisting symptoms of otolithic dysfunction, manifested by an ocular tilt reaction. Left internuclear ophthalmoplegia and left Horner syndrome were also present. These findings were consistent with the hypothesis that lower brainstem ischemia can generate room tilt illusion (9,10).

It has been proposed that room tilt illusion is caused by disturbed coordination of visual and vestibular-otolith pathways (1,2,11). The integration of visual and otolitic inputs might be influenced either directly at the level of the medulla or indirectly at the site of integration in the posterior parietal cortex (1). It has been shown that to create a neural image of visual surroundings, the posterior parietal cortex integrates three kinds of signals: visual information, vestibular information originating from otolitic inputs, and eye-position information (12–14). We should also consider the possibility that signals originating from changes in head position may affect the process of visual-vestibular integration, one coming from neck proprioception and the other from the integration of head velocity signals (15,16). In our patient, the illusion could be evoked by abruptly facing upward and stopped by forcibly bowing the head forward. This phenomenon indicates an indirect influence of peripheral vestibular inputs on central perceptual pathways (8). Thus, our patient provides evidence of a visual-vestibular interactive mechanism participating in the room tilt illusion. Cerebral and inner ear blood flow could vary with head position, but we presume that the most likely change related to the emergence of the room tilt illusion is in vestibular information arising from the otoliths.

REFERENCES
Migraine-like Visual Hallucinations as the Presenting Manifestations of Focal Seizures in Neurocysticercosis

Sanjeev Jha, MD and Rajesh Kumar, MD

Abstract: We report three patients with visual hallucinations as the initial manifestations of neurocysticercosis (NCC) in whom migraine was the first diagnosis. The correct diagnosis was suspected when electroencephalograms were abnormal and was confirmed by characteristic brain imaging. The visual hallucinations ceased promptly after treatment with antiepileptic and anti-NCC medications. We caution that NCC may present with focal seizures manifesting as visual hallucinations with features of migraine.

Finding no ocular abnormalities, an ophthalmologist referred the patient to a family physician who diagnosed migraine and treated her for this. When there was no response to beta-blockers and triptans, psychiatrists were consulted who prescribed anxiolytics for a presumptive diagnosis of anxiety neurosis. When there was still no relief, a neurologic consultation was undertaken.

An electroencephalogram (EEG) revealed epileptiform discharges and brain MRI revealed a ring-like lesion in the occipital region with a prominent scolex (Fig. 1). A presumptive diagnosis of NCC was made. Results of hematologic and biochemical investigations, including analysis of the cerebrospinal fluid, were normal. Perimetry revealed no visual field defects.

She was treated with 15 mg/kg/day carbamazepine; 15 mg/kg/day albendazole, and 1 mg/kg/day prednisone for 1 month. The hallucinations stopped within 4 days of starting treatment. She continues to be symptom-free and seizure-free after 8 months.

Case 2

A 28-year-old man presented with a 1-year history of episodes of sudden diplopia, vertigo, and vomiting. The frequency of these episodes was 2–6 per day. There was no tinnitus, hearing impairment, convulsion, or impairment of consciousness. Migraine was diagnosed, and he was treated with cinnarizine and betahistine to which he responded. He remained asymptomatic for 3 weeks, when he again developed diplopia. At the same time he reported seeing distorted multicolored zigzag lines lasting for 30–45 seconds followed by mild headache, nausea, and occasional vomiting for 30–60 minutes. The frequency of these episodes increased to 3–4 per week as headache and vomiting also increased.

Atypical migraine was again diagnosed, and he was given beta-blockers and flunarizine by a family physician, but there was no improvement. Complete ophthalmologic and neurologic examinations were normal, including formal visual fields. Results of hemogram, blood chemistry analysis, electrocardiography, and echocardiography were normal. An EEG revealed generalized paroxysmal epileptiform discharges. Brain MRI revealed multiple high signal ring-like lesions scattered bilaterally throughout both cerebral hemispheres (Fig. 2). Lesions in the right caudate, right
thalamus, and bilateral occipital areas were large with perilesional edema. Some lesions were cystic and contained a scolex. The enzyme immunoassay for NCC in the cerebrospinal fluid (CSF) was positive. CSF protein was elevated at 68 mg/100 mL, but glucose was normal at 58 mg/100 mL, and cell count was normal.

He was treated with 15 mg/kg/day carbamazepine, 15 mg/kg/day albendazole, and 1 mg/kg/day prednisone for 30 days. The frequency of hallucinations decreased after 2 weeks, and there was no further vomiting. Prednisone was discontinued after diplopia subsided. He continues to be symptom-free at follow-up after 5 months.

Case 3

A 41-year-old man presented with a 3-month history of seeing balls of fire jumping in front of his right visual field. These balls were multicolored, mainly bright red and yellow, and lasted for 15–30 seconds. The frequency of these episodes was 2–3 per week. Each episode was followed by an intense headache located mainly posteriorly. There were no associated convulsions or impairment of consciousness. There was no previous history of fever or exposure to drugs or toxins.

Visual acuity and visual field testing were normal. There was early optic disc edema (papilledema) in both eyes. Otherwise, the neuro-ophthalmologic and general physical examinations were normal. Results of the hemogram and blood chemistry analyses, including a thyroid profile, were normal. An EEG revealed paroxysmal generalized epileptiform discharges. A brain CT scan revealed multiple ring-enhancing granulomas and various stages of NCC in both cerebral hemispheres, including the occipital region (Fig. 3).

Acetazolamide at a dose of 375 mg/day and 20 mg/kg/day sodium valproate were administered for 10 days. The patient had become symptom-free, and the papilledema had disappeared when he reported for a follow-up examination 3 months later.

**DISCUSSION**

Our three patients with NCC presented with visual hallucinations as manifestations of seizures of occipital lobe origin. Lesions of NCC were found on brain imaging in the occipital region. The diagnosis of NCC in these patients was confirmed on the basis of clinical, biochemical,
FIG. 3. Case 3. Axial post-contrast CT reveals multiple ring-enhancing lesions, including one in the left occipital area.

radiologic, immunologic, and epidemiologic criteria (5) after excluding other etiologies mimicking NCC, such as tuberculous, fungal, or toxoplasma granulomas.

Seizures are the most common presenting manifestations of parenchymal NCC, occurring in 50–80% of patients (6,7). Potential mechanisms for the seizures are an inflammatory reaction to the parasite or mass effect (7,8). The seizures may consist solely of visual hallucinations, as occurred in our patients. The hallucinations may be elementary (occipital lobe origin) or complex (temporal lobe origin). The EEG is especially useful in showing the typical anterior sylvian abnormalities associated with seizures arising in the temporal lobe. The epileptogenic focus may be occipital with spread to the temporal lobe leading to clinical manifestations suggestive of temporal lobe origin. Independent contralateral temporal interictal and ictal discharges may also be found (9). Progress to temporal lobe structures is different and consistent with symptomatic occipital lobe epilepsy (10). The phenomenon of occipital lobe seizures spreading into anterior parts of the brain, primarily temporolimbic structures, has been well described on the basis of depth electrode recordings (9,11–14).

Seizures manifesting strictly as visual hallucinations in many patients are initially misdiagnosed as migraine with aura, basilar migraine, or acephalgic migraine (15). Although the visual hallucinations of occipital seizures and those of the migraine aura have common features, they can be differentiated.

The visual hallucinations of occipital seizures are mainly colored with circular patterns and often last for mere seconds (15). They often appear in the periphery of the temporal visual hemifield, becoming larger and frequently moving horizontally toward the midline (16). They are frequent, often occurring daily, and may be accompanied by eye and head deviation, illusions of eye movement, and repetitive eyelid closure or fluttering (13,14,17). Symptoms may progress to impairment of consciousness and generalized tonic-clonic activity (2). None of our patients reported blindness during the seizure episodes, but blindness may occur from the beginning (15). Associated headache may be ictal or postictal. Ictal headache is mild and rare. Postictal headache often associated with vomiting is frequent and lasts for 30 minutes–1 hour.

The visual auras of migraine start with predominantly flickering white linear and zigzag patterns in the center of the visual field and gradually expand over minutes toward the periphery of one hemifield, often leaving a temporary scotoma (18). They rarely occur as often as the hallucinations of occipital seizures (15). They may be associated with or progress to unilateral dysesthesias, hemiplegia, or dysphasia. Impairment of consciousness and convulsions are exceptional (2). Associated headache is typically unilateral, pulsating, and severe and is often associated with nausea and photophobia lasting for 4–72 hours.

Although migraine and epilepsy are distinct conditions with separate pathophysiologic mechanisms, they are found together in many patients and may even be causally related in some cases (19). Migraine attacks may follow partial complex seizures, particularly in adolescents and children. Seizures may follow migraine attacks; intercalated seizures are those that occur between the migraine aura and the headache phase (21). Seizures induced by a classical migraine aura are almost always occipital in origin (22). Migralepsy—an old term used for “a seizure that may be a composite of symptoms encountered in epilepsy and migraine”—has recently been reintroduced (23,24).

Basilar migraine may also be confused with seizures. This entity is usually seen in adolescent girls who subsequently develop common migraine (25). It is characterized by transient and fully reversible aura symptoms indicating focal dysfunction of the brain stem, the occipital lobes, or both, followed by headache (25–27). Symptoms include visual loss or flashing lights, vertigo, dysarthria, bilateral paresthesias, and transient loss of consciousness. Aura symptoms gradually develop over 4 minutes and last less than 1 hour (15). The post-event headache may last for several hours (20). Attacks are usually infrequent and tend to stop with the passage of time (15).
Neurocysticercosis

Case 2 in this study initially presented with frequent episodes of sudden vertigo, vomiting, and diplopia, suggesting basilar migraine or vestibular neuritis, a diagnosis supported by a response to vestibular sedatives. Reappearance of these features with prominent visual hallucinations was suggestive of basilar migraine, but the age, sex, and brief and frequent episodes of visual hallucinations did not support this diagnosis. The abnormal EEG, lesions in brain imaging, and response to antiepileptic medication supported the diagnosis of occipital seizures. In basilar migraine, paroxysmal EEG activity is not seen, but bilateral posterior slow waves may be seen for hours or days after an attack (28).

Visual hallucinations in patients from areas endemic for NCC should pose a high index of suspicion for NCC. These patients must be identified promptly so that effective treatment may be instituted early.

REFERENCES

Exotropia and Face Turn in Children With Homonymous Hemianopia

Sean P. Donahue, MD, PhD and Alden K. Haun, MD

Abstract: Four children developed homonymous hemianopia, exotropia with the deviating eye pointing in the direction of the field defect, and a face turn toward the side of the defect following complete third cranial nerve palsy after brain tumor resection, an in utero middle cerebral artery infarction, nonaccidental head trauma, and a hemispherectomy for an intractable seizure disorder. We present evidence that the exotropia and face turn are part of an adaptive mechanism to increase the usable visual field.


Many children who develop homonymous hemianopia during infancy also develop an anomalous head posture thought to be a compensatory mechanism to increase the available visual field (1). In reporting on a series of 10 patients with early-onset homonymous hemianopia and an anomalous face turn ipsilateral to the hemifield defect, Paysee and Coats (1) proposed that this posturing occurs in an effort to maximize visual function by using saccades into the non-seeing hemifield.

There have been reports of patients with congenital or early-onset homonymous hemianopia developing an exotropia (2,3). Hoyt and Good (4) have queried whether the exotropia is compensatory or simply an epiphenomenon due to the associated infantile neurologic disease often found in these patients.

We have studied four patients who developed homonymous hemianopia early in life. All had anomalous head posturing and an ipsilateral exotropia. In one patient with acquired third cranial nerve palsy and a homonymous hemianopia, the exotropia persisted despite full restoration of ocular motility. A second patient developed exotropia and a face turn after a hemispherectomy that produced a homonymous hemianopia. We present evidence that the development of exotropia in patients with anomalous head posturing and a homonymous hemianopia is an adaptive mechanism that serves to further expand the usable visual field.

CASE REPORTS

Case 1

A 4½-year-old boy had a right thalamic-temporal pilocytic astrocytoma resected at the age of 3½ years. The tumor involved the right optic tract. After tumor resection, he was noted to have a complete right third cranial nerve palsy with ptosis, ophthalmoplegia, and a dilated, poorly reactive right pupil. He developed hydrocephalus, partial complex seizures, and a left hemiplegia. He was treated with carboplatin and vincristine.

When he was examined by the pediatric ophthalmology service 8 weeks after tumor resection, he had best-corrected distance visual acuities of 20/40 in the right eye and 20/50 in the left eye. Visual acuity in the right eye was markedly decreased at near, suggesting poor accommodation from the third cranial nerve dysfunction. There was a 1 mm asymmetry in lid function with a narrower right palpebral fissure but no frank ptosis and no anisocoria. There was a 45 prism-diopter exotropia with a mild deficit of supraduction, infraduction, and adduction of the right eye. Ophthalmoscopy revealed optic disc pallor bilaterally and mild incyclotorsion of the right eye.

Neurologic examination showed a left hemiparesis. The patient could not cooperate for confrontation visual field testing on this visit. Over the next 2 months the right third cranial nerve palsy resolved completely, but the large-angle exotropia remained and became comitant. The patient developed a left face turn and began to fixate with the previously paretic right eye (Fig. 1). The patient was noted to have a dense left homonymous hemianopia on confrontation visual field testing. He has been followed for more than 2 years without a change in his examination or recurrence of tumor.
Homonymous Hemianopia


FIG. 1. Case 1. The patient has a left face turn, right eye (previously paretic eye) fixation, and exotropia.

Case 2

A 7½-year-old girl with a history of an in utero right middle cerebral artery stroke and left hemiparesis presented with the parents noticing that “her eyes were turning out.” Her primary physician and parents both reported that her strabismus was long-standing. Best-corrected visual acuity was 20/20 in both eyes. She had a 20 prism-diopter left exotropia, a left face turn, and a left homonymous inferior quadrantanopic defect on automated perimetry (Fig. 2). A right-beating nystagmus was present in all positions of gaze. It did not change on side gaze, and there was no null position in right gaze.

On neurologic examination, a left hemiparesis was found. Follow-up MRI revealed no new lesions, and the carbamazepine level at the time of presentation was normal.

At age 13, 5 years after having constant exotropia, the patient desired strabismus surgery because she was being teased by her schoolmates. The patient and her mother were both advised of the potential functional benefit of her exotropia. Nevertheless, she chose to proceed, and underwent a resect-recess procedure on her non-fixating left eye. Her vision was initially overcorrected to esotropia, but within 6 months she had developed a recurrent exotropia of 10–15 prism diopters, which has remained stable over 3 years of follow-up. Her anomalous head position has persisted.

Case 3

An 11-month-old girl had undergone a hemispherectomy at age 5 months for uncontrolled seizures. An MRI scan had demonstrated cortical neuronal migration abnormalities.

The child’s parents reported that she had developed an exotropia shortly after the hemispherectomy and preferred to fixate with her left eye. She had a right face turn that her parents had noticed shortly after surgery.

Examination at age 11 months demonstrated central, steady, and maintained fixation in each eye although there was a fixation preference for the left eye. She had a 20 prism-diopter comitant exotropia with full versions although detailed alignment measurements could not be performed. Confrontation visual field testing demonstrated a right homonymous hemianopia. The remainder of the examination was normal.

When last examined at age 3½ years, she continued to manifest a left eye fixation preference, no significant amblyopia, full versions, a comitant exotropia, a right face turn, and a dense right homonymous hemianopia.

Case 4

A 7-month-old girl with a history of severe head trauma due to child abuse at age 5 months was referred to the pediatric ophthalmology service for evaluation of her visual status. She could fix and follow bilaterally and had full ocular motility with a well-controlled esophoria. The pupillary, anterior segment, and dilated funduscopic examinations were normal. Confrontation visual field testing showed a left homonymous hemianopia. Neurologic evaluation showed a left hemiplegia.

On examination 7 months later, she had developed an intermittent 20 prism-diopter comitant left exotropia. A left face turn was first noted 6 months later. She has since been followed through the age of 2½ years and has maintained a comitant, poorly controlled, intermittent exotropia with a fixation preference for the right eye, a left homonymous hemianopia, and a left face turn.

FIG. 2. Case 2. Humphrey visual field testing shows a left homonymous quadrantanopia.
DISCUSSION

Children often develop anomalous head postures to compensate for visual or ocular motility impairments. Children with congenital nystagmus may develop a face turn to maintain their eyes in a null position. Patients with superior oblique palsy, Duane syndrome, and other paralytic and restrictive strabismus syndromes also typically have abnormal head postures.

The development of a face turn ipsilateral to a visual field defect has been described as a functional adaptation to early onset homonymous hemianopia (2,3). Zangemeister et al (5) hypothesized that this adaptive mechanism allows the use of large saccades to expand the useful peripheral visual field. In this situation, the patients adopt an ocular motor strategy of a large overshooting saccade into the blind hemifield followed by scanning back through the blind field. The face turn rotates the seeing field toward midline. Similar findings of anomalous head position with homonymous hemianopia were reported by Paysee and Coates (1), but only 1 of their 10 patients was exotropic.

Our four patients were collected consecutively and prospectively as they presented to the pediatric ophthalmology service. All four had previously acquired homonymous hemianopia early in life and developed ipsilateral exotropia (fixation preference for the contralateral eye) and a face turn toward the visual field defect. In two patients (Cases 1 and 4), the exotropia and face turn developed as other related neurologic problems (third cranial nerve palsy and head trauma) resolved, suggesting that the exotropia and face turn were both compensatory. In our Case 3, the exotropia and face turn became manifest after a surgical procedure that produced a homonymous hemianopia.

The exotropic eye of all four of our patients was on the side of the hemianopia, and, in addition, the child with the third cranial nerve palsy switched fixation to the paretic eye as his face turn developed. It is unlikely that all of these events would have occurred by chance alone, suggesting that the exotropia enhances visual function.

We believe that the development of an ipsilateral exotropia in patients with anomalous head posturing toward an ipsilateral homonymous hemianopia serves to expand the usable visual field (Fig. 3). The anomalous retinal correspondence created by the exotropia enlarges the available visual field, as the visual field defect becomes reduced because the exotropic eye is on the side of the homonymous hemianopia. As suggested by Zangemeister et al (5) and Paysee and Coates (1), large-amplitude saccades may also play a role in visual field expansion, as these saccades into the blind hemifield are a method of “scanning” the visual periphery. The best evidence for an expanded visual field would be to perform visual field testing under binocular conditions. The youth of three of our patients prevented us from doing this in a formal quantitative manner. However, functional enlargement of binocular visual fields in the exotropia-hemianopia syndrome has been previously reported (2,3,8).

An incomitant exotropia or a symmetric nystagmus with a null position could have produced the face turn we observed. However, only one of our patients had nystagmus (and no identifiable null position), and all four had lateral gaze comitance.

**FIG. 3.** Schematic explanation for visual field expansion with exotropia and face turn in patient with homonymous hemianopia. A. Patient with a right homonymous hemianopia. B. If the eye ipsilateral to the field defect is exotropic, the seeing field expands across the midline. C. A face turn toward the field defect increases the area of effective field when adaptive saccades are made.
The outward shift of the hemianopic border and reduction of the quantitative defect created by the exotropia requires the deviated eye’s localization of the image to have harmonious anomalous retinal correspondence (6). An alternative would be normal retinal correspondence with alternating suppression, but this would not produce an increase in usable visual field.

The exotropia in two of our patients was intermittent, and in Case 2 was associated with 200 arc-seconds of stereopsis. Perhaps expansion of the visual field is not required when attention is directed centrally and is superseded in that instance by the need for high-grade stereopsis. However, the exotropia would become manifest when the patient is searching the environment and needs an expanded field rather than central binocularity.

In commenting on a case of exotropia and homonymous hemianopia (7), Hoyt and Good (4) proposed that an exotropia in patients with hemianopia may be an epiphenomenon and not compensatory because of the association of exotropia with infantile neurologic disease. Similar comments have been made by Good et al (8). However, our Cases 1, 3, and 4 suggest that the exotropia is adaptive. Case 1 showed complete resolution of all the ocular motility defects associated with third cranial nerve palsy except for the exotropia, which became constant, and he switched his fixation to the previously paretic right eye. The exotropia and field defect seen in Case 3 developed after the hemispherectomy that produced the homonymous hemianopia. Case 4 developed an exotropia from an earlier esophoria, and it developed months after the visual field defect occurred. The recurrence of the exotropia after strabismus surgery (Case 2) is so common that it cannot be attributed to the homonymous hemianopia.

Other reports have used confrontation visual field tests to document the visual field defect. We believe that our Case 2 is the first to have formal quantitative perimetry. The defect is particularly dense, but notably incomplete, especially superiorly. The extent and congruency of the homonymous defect required to produce the hemianopia-exotropia-face turn syndrome, however, remain unresolved and await further evaluation of additional patients.

In summary, we have observed four patients with early-onset homonymous visual field defects who have an ipsilateral exotropia and an ipsilateral anomalous face turn. None had an incomitant strabismus or nystagmus with a null point. All have remained stable through years of follow-up. We believe that the face turn and the exotropia are both functionally beneficial to increase the usable visual field. Surgical correction for these patients may adversely affect these adaptive mechanisms; this fact should be considered when one is formulating management options (9).

REFERENCES

Reversible Tonic Pupils

Caroline A. A. Hulsman, MD, PhD and Christine T. Langerhorst, MD, PhD

Abstract: A 36-year-old man with a remote history of Hodgkin lymphoma and a recent history of non-Hodgkin lymphoma (NHL) developed tonic pupils and absent deep tendon reflexes in the lower extremities. One year later, pupils were normal except for slight iris segmental contraction to light. Over the next 2 years, the patient remained asymptomatic, and pupils remained unchanged. The NHL went into remission, and no other neurologic manifestations appeared. This is the first report of reversible tonic pupils. They may have a pathogenesis different from that typically seen in irreversible tonic pupils.


A tonic pupil is characterized by a poor to absent constriction to light but a normal to strong constriction to a near stimulus (1). A tonic pupil dilates slowly and is supersensitive to topically applied cholinergic agents. An accommodation paresis is often present. When hyporeflexia or areflexia of the lower limbs is also found, it is called Adie syndrome, which is reported to be a chronic phenomenon. To our knowledge, Adie syndrome has not been previously documented as reversible. We report a single case of transient bilateral tonic pupils with areflexia of the lower limbs in a patient with lymphoma.

CASE REPORT

A 36-year-old white man was referred to our neuro-ophthalmology clinic by the departments of neurology and internal medicine for pupillary abnormalities.

The patient had had Hodgkin disease at age 16 with complete remission after treatment with three cycles of mechlorethamine, vincristine, procarbazine, and prednisone, together with total lymph node irradiation, which led to hypothyroidism. At age 33, he was found to have a large B-cell non-Hodgkin lymphoma (NHL) of the spine, considered secondary to the treatment of Hodgkin disease. For the NHL, he was treated with cyclophosphamide, doxorubicin, vincristine, and prednisone. Several months later, a suspected NHL in the lung was treated with focal irradiation.

At the time of our examination 1 year later, medication was limited to 0.1 mg/day levothyroxine. He complained of headache, blurred vision in the right eye, and a large pupil in the right eye for 1 week. Uncorrected visual acuity was 20/20 in both eyes. In a normally illuminated room, the right pupil measured 7 mm, and the left measured 4 mm. In response to direct light, the right pupil constricted to 5 mm and the left pupil to 2.5 mm. The right pupil constricted further to a near stimulus. The pupil redilated slowly, whereas the left pupil redilated briskly. At slit lamp examination bunching of the pupillary border was observed over 3 clock hours in the inferior part of the iris of the right eye. No structural abnormalities of the iris were present. Otherwise results of the slit lamp and opthalmoscopic examinations were normal. Visual fields, tested by confrontation, were normal, and there were no abnormalities of eyelids, eye movements, or ocular alignment.

After application of 0.1% pilocarpine to both eyes, the right pupil constricted to the same level as the left pupil (4 mm), which showed no constrictive effect.

Five weeks later, the patient returned with the same complaints about the left eye. The right eye showed the same signs as during the first visit. The left pupil now did not constrict to light but did have a normal near response and showed segmental constriction at the slit lamp. Deep tendon reflexes of the lower limbs were absent, but there were no other neurologic abnormalities. We prescribed reading glasses and topical 0.1% pilocarpine.

On a follow-up visit 1 year later, the patient was asymptomatic. He did not need his reading glasses anymore, his uncorrected visual acuity was 20/20 in both eyes, and both pupils were of equal and normal size. They constricted normally to light and a near stimulus, although slit lamp examination still showed slight segmental contraction of the iris to light in both eyes. At that time, a recurrence of NHL in the duodenum was treated with chlorambucil and prednisone. Two years later, the ophthalmic examination remained unchanged. Biopsies of the duodenum showed no evidence of lymphoma.
DISCUSSION

Tonic pupil is a benign disorder, occurring mostly as an isolated manifestation and rarely in orbital trauma, retinal photocoagulation, inflammation, infection, infiltrative processes, ischemia, or dysautonomia associated with malignant disease and amyloidosis (1). It is caused by damage to the postganglionic parasympathetic pupillomotor fibers. The incidence is 4.7 cases per 100,000 persons per year (1). Tonic pupil is unilateral in 80% of cases. When it is bilateral, each eye is usually affected in separate episodes, with the second eye becoming affected with a frequency of 4% per year (2). Within months to years of onset, the affected pupil becomes smaller, continuing to fail to constrict to light but constricting in response to a near stimulus. The accommodation paresis usually recovers.

The typical near-light dissociation is explained by the hypothesis that dysfunction or loss of a certain number of ciliary ganglion fibers has a smaller effect on accommodation than it has on light reaction because the number of fibers that regulate accommodation is much larger than the number regulating the pupil constriction to a light stimulus. Reinnervation of the iris sphincter by surviving axons of the accommodative ciliary nerve fibers may play a role in allowing pupillary constriction to a near stimulus (1).

The recovery of the pupillary light reaction in our patient is very unusual. Perhaps the pathogenesis is different from that in the typical tonic pupil (2–4). In our case, the pupillary light response might have recovered because fibers were not destroyed but merely rendered dysfunctional. The fact that the pupils of our patient returned to normal size, rather than becoming smaller in time as occurs in most cases of tonic pupil, suggests that pupilloconstrictor fibers may have regenerated.

In our patient, no signs of lymphoma were observed in the iris or in any other part of the eye, and the malignancy was in remission at the time of occurrence of the tonic pupils. The tonic pupils may have been unrelated to the lymphoma. However, neuropathic tonic pupils have been described as part of a generalized autonomic neuropathy, which can occur as a paraneoplastic manifestation. Tonic pupils have been described in a patient with carcinomatous polyneuromyopathy secondary to metastases of an unknown tumor (3) and in patients with the paraneoplastic polyneuropathy associated with type 1 anti–neural nuclear autoantibodies (ANNA-1, anti-Hu) secondary to small cell lung cancer (5). In our patient, no polyneuropathy was present. However, the tonic pupils may have been a very local manifestation of a paraneoplastic syndrome.

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Tonic Pupil as the Presenting Sign of Relapsed Acute Myeloid Leukemia

A 23-year-old woman complained of photophobia, lacrimation, and redness of the left eye of 1 week’s duration and a dilated left pupil. Acute myeloid leukemia (AML) had been diagnosed 5 years earlier and treated with a stem cell transplant. She had developed graft vs host disease (GVHD) affecting her skin and had undergone psoralen plus UVA (PUVA) treatment. The AML had been in remission for 3 years before her ophthalmic visit. Medications included acyclovir, fluconazole, penicillin, cyclosporine, and mycophenolate. Systemic corticosteroid treatment had recently been discontinued.

Best-corrected visual acuities were 20/20 in the right eye and 20/40 in the left eye, improving to 20/30 with pinhole. In the left eye, the palpebral fissure was slightly narrow but with normal levator function, the tear break-up time was reduced, and there was punctate staining of the cornea.

The pupils measured 2 mm in the right eye and 4 mm in the left eye in minimal illumination. On bright light stimulation with the indirect ophthalmoscope light, the right pupil constricted to 1 mm and the left remained at 4 mm. After stimulation by a near target the left pupil also constricted to 1 mm. The left eye showed vermiciform movements of the iris on slit lamp examination. Dilute pilocarpine (0.125%) was then instilled in both eyes. After this both pupils measured 2 mm, demonstrating hypersensitivity of the left pupil. She was orthophoric and had a full range of ocular movements. Posterior subcapsular lens opacities were present in both eyes. Ophthalmoscopy was normal. The punctuate epitheliopathy of the cornea was attributed to GVHD and the cataracts to the use of systemic corticosteroids. Left tonic pupil was diagnosed. Lubricants were prescribed for the epitheliopathy.

Two days later, she returned complaining of blurred vision. Best-corrected visual acuities were 20/80 in the right eye and 20/40 in the left eye. There was no change in the anterior segment findings of either eye. Ophthalmoscopy showed localized elevation of the retina in the macular region in both eyes. B scan ultrasound showed thickening and irregular elevations of the choroid in both eyes (Fig. 1). Fluorescein angiography showed pinpoint areas of hyperfluorescence of increasing brightness in the macular region of both eyes.

Blood tests showed an elevated white cell count, indicating relapse of leukemia. Brain and orbit MRI showed only faint mucosal thickening of the sinuses. Chemotherapy was begun. The leukemia could not be controlled, and she subsequently died of systemic complications.

Tonic pupil can be caused by Adie syndrome, systemic neuropathic diseases, or local lesions (1). Adie syndrome is characterized by tonic pupil and disturbance of deep tendon reflexes without evidence of local ocular or orbital disease or generalized peripheral or autonomic system dysfunction. Orbito-ocular causes of tonic pupil include inflammation, infection, or infiltration that affects ciliary ganglion or the ciliary nerves in the retrobulbar region or in the suprachoroidal space. Tonic pupil has been reported in siderosis caused by retained intracocular foreign body (2); injury to the final cholinergic fibers within the suprachoroidal space was postulated as the likely pathologic mechanism. Postganglionic denervation by damage within the suprachoroidal space has also been reported with retinal detachment surgery using explants (3) and after laser photocoagulation for diabetic retinopathy (4).

Leukemia can cause tonic pupil by direct infiltration of the orbit or the choroid. However, postganglionic nerve injury at the level of the eye in choroidal cancer has been reported only once (5). In our patient, there was no imaging evidence of orbital infiltration at presentation. The ultrasound study showed extensive choroidal thickening and irregularity. The fluorescein evidence of pinpoint leaks and serous retinal detachment indirectly indicated dysfunction of the retinal pigment epithelium. A similar phenomenon...
caused by choroidal infiltration has been reported (6). Hence it is likely that the damage to the ciliary nerves occurred at the suprachoroidal level.

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Generalized Myasthenia Gravis Triggered by Cataract Surgery

There have been many case reports describing onset of myasthenia gravis (MG) after cardiac surgery (1–3) and after administration of neuromuscular blocking agents in preparation for surgery (4). We describe a patient in whom severe generalized MG developed immediately after cataract surgery, requiring thymectomy and long-term immunosuppressive therapy.

A 52-year-old right-handed white man developed progressive weakness 1 day after outpatient cataract surgery on the right eye. His past medical history was significant for insulin-dependent diabetes treated with an insulin infusion pump. He had diabetic peripheral neuropathy.

Before surgery, he reported no other neurologic symptoms. The cataract surgery was uncomplicated, and routine topical analgesics had been applied on the eye before the procedure. The patient noticed nothing unusual until he removed the eye patch the day after surgery and experienced diplopia followed by bilateral ptosis. Over the next 2 weeks, he noted progressive fatigue and limb weakness. A Tension test performed 3 weeks after surgery showed subjective and objective strength improvement, and pyridostigmine and prednisone were started. One week later, he developed neck weakness and difficulty swallowing and was hospitalized.

On admission, he had 4 mm of ptosis bilaterally. The right eye had no movement in any direction. The left eye had 80% adduction and abduction and full verticalduction. He was hoarse and had difficulty swallowing liquids. He had 4/5 weakness in distal and proximal muscles. His reflexes were 1+ throughout. Plantar reflexes were flexor. Sensory signs included bilateral decreased temperature, vibration, and joint position sense distal to the knees.

Results of laboratory studies were negative for acetylcholine receptor binding and blocking antibody, anti-striated muscle antibody, anti-muscle-specific tyrosine kinase (MuSK) antibody, serum cytomegalovirus (CMV) IgG and IgM, and anti-ganglioside GD1a IgG and IgM antibody. Results of a paraneoplastic workup were negative. A chest CT scan was negative for thymoma, and cerebrospinal fluid (CSF) showed a red blood cell count of 0, white blood cell count of 1, glucose of 157 mg, and protein of 89 mg.

Slow repetitive nerve stimulation (3 Hz) of the bilateral median nerve at rest and 1 minute after exercise showed compound muscle action potential (CMAP) amplitude decrements of 35% and 20%, respectively, consistent with a diagnosis of neuromuscular junction disorder. The baseline CMAP amplitude was normal without an incremental response of CMAP amplitude after 10 seconds of maximum isometric contraction, making it less likely to be a presynaptic condition. Sensory nerve action potentials were absent, indicating a polyneuropathy. Surprisingly, the patient had moderate to severely prolonged CMAP onset latencies with decreased conduction velocity in all extremities and preserved CMAP amplitudes, indicating a demyelinating polyneuropathy, which is unlike the findings seen in typical diabetic neuropathy.

The patient was treated with a course of plasmapheresis and his bulbar symptoms improved. Three months after his initial symptoms, he underwent thymectomy, with the specimen showing normal thymic tissue. With 60 mg prednisone, 80 mg pyridostigmine 3 times/day, and 250 mg mycophenolate mofetil 2 times/day, he continues to have binocular oblique diplopia that is worse in up-and-left gaze and is ambulatory with minimal assistance.

It is rare to identify a trigger for the onset of MG. With respect to cardiothoracic surgery (1–3), it has been presumed that manipulation of thymic remnants provided a trigger for autoimmune damage. It is possible that damage induced during the surgical procedure could induce a new wave of autoantibody production that is not readily subject to immune regulation in susceptible individuals.

A well-documented effect of neuromuscular blockade agents such as vecuronium, which are administered during tracheal intubation, is to unmask undiagnosed MG. The diagnosis is made when patients fail to maintain adequate...
spontaneous ventilation after the procedure (4,5). Subsequently, it is discovered that such patients have a history of ptosis, diplopia, dysphagia, dysarthria, fatigue, and weakness.

We postulate that the cataract surgery itself or local anesthetics triggered an autoimmune response or aggravated a preexisting subclinical MG in this patient.

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Benztropine-induced Esotropia and Mydriasis

We recently examined a patient with esotropia and dilated pupils who had received haloperidol and benztropine mesylate to treat Tourette syndrome. Immediate resolution of the esotropia and mydriasis after discontinuation of benztropine mesylate indicates a causal relationship. This is the first report of esotropia induced by anticholinergic medication.

A 16-year-old girl who had pseudohypoparathyroidism and mild mental retardation began to take 3 mg haloperidol and 2 mg benztropine mesylate per day for a diagnosis of Tourette syndrome, which had manifested with involuntary vocalization, snorting, frequent troublesome motor behaviors, and occasional aggressive impulses. Five days after starting the medications, she experienced sudden dizziness, diplopia, and blurred vision. There was no preceding systemic or ocular infection or physical or psychic shock. She had no history of strabismus or visual dysfunction.

Seven days after she started the medications, neuro-opthalmologic examination revealed a visual acuity of 20/20 in both eyes, esotropia of 35 prism-diopters when fixating a distant (20-foot) target (Fig. 1), and esotropia of 45 prism-diopters when fixating a near (14 inch) target. Refraction with cycloplegia showed no hyperopia. Ocular ductions and versions were full. Anterior and posterior segments were normal with clear and sharp disc margins in both eyes. Both pupils were enlarged at 7 mm and unreactive to light and near stimuli (Fig. 2). The dilated pupils did not constrict in response to 0.1% or 1.0% solutions of pilocarpine eye drops (Fig. 2). There were no other neurologic findings.

Results of routine laboratory tests, including complete blood cell count, routine blood chemistry analyses, urinalysis, and chest x-ray, were negative. Brain and orbital MRI showed small symmetric calcifications of the basal ganglia.

The benztropine mesylate was discontinued, and the diplopia, dizziness, and esotropia disappeared within 2 weeks. A follow-up ophthalmologic evaluation 2 months later disclosed no esodeviation by alternate cover tests, but a reduced fusional divergence amplitude of 4 prism-diopters (normal 6–8 prism-diopters). The pupils were normal in size and reactivity.

Anticholinergic medications may cause dry mouth, bladder dysfunction, constipation, impaired cognition, and visual disturbance. With repeated doses of certain anticholinergics, reduction in the near point of accommodation has been reported (1). Benztropine mesylate, a tertiary amine muscarinic receptor antagonist frequently used to antagonize the parkinsonian side effects of antipsychotics, may impair accommodation and near visual acuity, especially when used with neuroleptics (1,2).

Various anticholinergic drugs, including amitriptyline, oxybutynin, propantheline, and atropine, can cause pupillary dilatation (3). In children, topical anticholinergics increase the accommodative convergence-to-accommodation ratio transiently and exacerbate an underlying esotropia (4).

FIG. 1. Comitant esotropia is present with distant fixation.
Moreover, esotropia may develop after anticholinergic eye drops without preexisting esotropia (5). The synkinetic near triad consists of accommodation, convergence, and pupillary constriction. The ratio of convergence to accommodation may increase with anticholinergics due to partial block of accommodation. To see a near target in the setting of blocked accommodation, children would increase accommodative effort, resulting in increased convergence. Too much convergence may cause esotropia.

Nonetheless, the mechanism by which benztropine mesylate might cause esotropia remains unclear. The preserved ocular versions during the period of esotropia suggest that it was neither paralytic nor restrictive in origin. Furthermore, decompensation of a preexisting, well-compensated esotropia by benztropine mesylate seems unlikely because the patient never had a history of esotropia and showed orthophoria after discontinuing the medication. Increased intracranial pressure (ICP) may produce divergence paralysis without evidence of a sixth cranial nerve palsy (6). However, our patient showed no symptoms or signs of increased ICP and had full ductions andversions. One possibility is that the esotropia in our patient was due to a temporary disruption of binocular function.

The mydriasis in our patient is also interesting. Whereas systemically administered anticholinergics do not alter pupillary diameter in dogs (7), they may cause mydriasis in men (7). Failure of 0.1% and 1% pilocarpine drops to contract the pupils of our patient indicates that the iris sphincter had been blocked by an anticholinergic agent.

The reason for the rare occurrence of esotropia in patients using anticholinergics remains unknown. The reduced fusional divergence amplitude, found after the resolution of mydriasis and esotropia in our patient, may be a prerequisite for development of esotropia when anticholinergics are used. Alternatively, because strabismus (esotropia) is common in children with developmental disabilities, including mental retardation and cerebral palsy (8), the combination of Tourette syndrome and pseudohypoparathyroidism with mental retardation may have contributed to the occurrence of the ophthalmic manifestations in our patient.

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Idiopathic Intracranial Hypertension in a Transgender Man

We report a case of idiopathic intracranial hypertension (IIH) in a transgender man. To our knowledge, no such case has been described previously.

A 33-year-old man presented to the neuro-ophthalmology clinic at the University of Florida in January 2007. He was complaining of headaches and blurred vision. IIH had been diagnosed 8 months earlier, and he was treated
FIG. 1. Optic disc edema is present in both eyes.

with 1,500 mg/day acetazolamide. He reported being a transgender woman-to-man who had undergone bilateral mastectomies and testosterone treatment that had been discontinued 18 months earlier.

Our examination disclosed a patient who weighed 168 lbs with height of 5 feet 3 inches. Blood pressure was 118/72 mm Hg with a pulse of 84/min. Best-corrected visual acuities were 20/15 in each eye. Color vision was normal by Ishihara plate testing. Ophthalmoscopy showed optic disc edema in both eyes (Fig. 1). Humphrey visual fields showed nerve fiber bundle defects and enlarged blind spots in both eyes (Fig. 2). Results of a CT angiogram with attention to the venous phase was normal. A lumbar puncture disclosed an opening pressure of 300 mm H₂O with normal constituents.

Because of side effects from acetazolamide, 80 mg/day furosemide was substituted for acetazolamide. For headache control, he was treated with 150 mg/day topiramate. On a follow-up 1 month later, visual field defects had improved. However, 2 months later, the visual field defects worsened, and he underwent an optic nerve fenestration in the right eye. One week postoperatively, visual field defects had improved in the left eye, but the right eye remained stable. On month later, visual field defects had improved in both eyes.

IIH is found most commonly in overweight women in their reproductive years. It may also be caused by dural sinus thrombosis (5,6), a reduction in corticosteroid therapy, or hormonal imbalance (7–10), vitamin A, anabolic corticosteroids, tetracycline, lithium, and pregnancy (11–13). Our patient had prior use of testosterone. Despite the availability of transgender medicine for decades, we were unable to find a published report of IIH in patients who change gender.

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Simultaneous Ischemic Optic Neuropathy and Third Cranial Nerve Palsy in Giant Cell Arteritis

We report for the first time the concurrence of ischemic optic neuropathy and third cranial nerve palsy in a case of histologically proven giant cell arteritis (GCA).

An 87-year-old woman was admitted to the hospital with a 4-week history of pain on her scalp, under her chin, and in the occipital area and neck. In addition, she had jaw claudication, which gradually increased in intensity. One day earlier, the patient simultaneously developed sudden profound vision loss and ptosis of the right eye. She had lost the vision in the left eye many years earlier from direct trauma.

Our examination revealed a best-corrected visual acuity of 20/200 in the right eye and no light perception in the left eye. The right pupil measured 5 mm in dim illumination and did not constrict to direct light. The left pupil was irregular, measured about 2.5 mm, and did not constrict to direct light. The right upper lid had 3 mm of ptosis. In the right eye, abduction was normal, but adduction, supraduction, and infraduction were absent. Ophthalmoscopy of the right eye revealed mild optic disc swelling. Evaluation of the left eye could not be done because of the history of trauma. Pulsations of the right temporal artery were not palpable, and those of the left temporal artery were feeble. There was scalp tenderness.

The erythrocyte sedimentation rate was 55 mm/h (normal value <15 mm/h), C-reactive protein (CRP) was 8.3 mg/L (normal value <6 mg/L), and platelet count was 625,000/μL (normal value 142,000–424,000/μL). Brain MRI was normal. On color duplex ultrasonography, no fluximetric alterations of carotid and vertebral arteries were seen.

The following day, biopsy of the right temporal artery showed marked inflammation and intimal fibrosis (Fig. 1). The media contained lymphocytes and giant cells. Fragmentation of the internal elastic lamina of the artery was evident. A diagnosis of giant cell arteritis was made and treatment with 50 mg oral prednisolone was started. Within a few days, the headache disappeared. The medication was continued at the same dose for 20 days, after which the dose was tapered. Three months after the corticosteroid treatment was started, the features of third cranial nerve palsy had disappeared except for a dilated unreactive pupil. The vision loss persisted.

Impairment of the third, fourth, or sixth cranial nerves has been reported in only 2% of patients with GCA (1–8). This case illustrates the fact that ischemic optic neuropathy and third cranial nerve palsy may be coincident manifestations of GCA.

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More than 6,000 abstracts were presented at the annual meeting of the Association for Research in Vision and Ophthalmology (ARVO), Fort Lauderdale, FL, May 6–10, 2007. Available at www.arvo.org, the abstracts are referenced by program number (#).

This year the focus was on the 'Aging Eye.' In their keynote address, William Novelli, director of American Association of Retired Persons (AARP), and Paul Lee, MD, of Duke University emphasized the rising ophthalmic health care costs in the aging population and the importance of early recognition and treatment.

The Proctor Medal was awarded to Nicolas Bazan, MD, PhD, for his work on neuroprotection signaling in retinal pigment epithelium. The Weisenfeld Award went to David Guyton, MD, for his seminal work on cyclovertical strabismus. The Friedenwald Award winner was Ilene Gipson, PhD, who presented her work on the importance of the ocular surface. The Cogan Award was given to Wolfgang Drexler, PhD, for his pioneering work on optical coherence tomography (OCT).

**NEUROPROTECTION**

In a placebo-controlled animal study using pigmented rabbits, a single dose of oral memantine was found to normalize the sweep visual evoked potential (VEP) deficit after an acute elevation of intraocular pressure (IOP) (#96). Prophylactic administration of simvastatin was shown to produce neuroprotective effects against ischemic reperfusion-dependent deficits in retinal function demonstrated by using a rat acute glaucoma model and quantitated by recording scotopic electroretinograms (ERGs) before and 1 week after the ischemic insult (#208). Brimonidine, an $\alpha_2$ receptor agonist, provided rescue and protection from stress-induced loss of mitochondrial membrane production and reactive oxygen species (ROS) production in rat retinal ganglion cells (RGCs). This study suggests that brimonidine exerts a direct protective effect on RGCs apart from its role in lowering IOP (#620).

Intravitreal injections of activators of SIRT1, an enzyme involved in cellular stress resistance and survival, attenuated RGC loss in a dose-dependent manner in a mouse model of optic neuritis. The neuroprotective effect was blocked by sirtinol, a SIRT1 inhibitor. This model suggests that SIRT1 activators may be beneficial as additives with current multiple sclerosis (MS) immunomodulatory therapies (#563).

Bacterial DNA was shown to provide neuroprotection after optic nerve crush injury by suppressing CD4 and CD5 regulatory T cell activities (#1539). NAP is an 8-amino acid peptide derived from activity-dependent neuroprotective protein and plays an important role in neuronal differentiation and survival of neurons. Injected intraperitoneally in a retinal ischemia rat model, NAP increased the number of surviving RGCs by 30%–40% after optic nerve crush and retinal ischemia in vitro (#565). Tempol (4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl), a superoxide dismutase mimetic, attenuated RGC loss in an optic nerve crush trauma model (#3286).

**OPTIC NEUROPATHY**

Rodent anterior ischemic optic neuropathy (rAION) induced in Wistar rats showed a regional loss of RGCs by apoptosis (#4197). Although some RGCs die soon after induction of AION, demonstrable apoptosis occurs for nearly 1 month after induction with two major peaks of cell death. The earliest apoptotic peak is the longest, with a major loss of cells occurring between 7 and 15 days. Apoptosis was nearly complete by 31 days, suggesting that a measure of retinotopic organization occurs in the rodent optic nerve as in primates and humans (#4197). Because there are considerable differences between rodent and primate retina and optic nerves, a primate model of nonarteritic anterior ischemic optic neuropathy (pNAION) that closely resembled clinical NAION was produced using rhesus monkeys (#4410). In a clinical study, investigators determined that the severity of visual field loss (mean deviation) in the first eye was a risk factor for developing NAION in the second eye (#3172).

Nuclear gene OPA1 encodes a mitochondrial inner membrane protein, a GTPase in the dynamin family, and
maintains the integrity of mitochondrial inner membrane. OPA1 is expressed in all retinal layers including the RGC. Immunohistochemical and electron microscopic studies on mouse retina, optic nerve, and tracts were performed using OPA1 and ATP synthase antibodies. The mitochondrial structure in RGC axons posterior to the lamina cribrosa is tubular with dark content. Anterior to the lamina cribrosa, mitochondria are round with clear content. The transformation from spherical to tubular mitochondria involves OPA1 function. OPA1 activity is also important in distribution of mitochondria along the axon during retinal development and maintenance of the mitochondrial membrane potential. A study found that OPA1 in the cell soma is required to prevent apoptosis (#1540). In a clinical study, retinal nerve fiber layer (RNFL) thickness measurements using OCT were performed in 30 patients with OPA1-dominant optic atrophy (DOA), showing that OPA1 influences the anatomical conformation. Findings included decreased nerve fiber layer thickness in all four quadrants around the optic nerve, decreased disc area, vertical and horizontal disc diameter, decreased rim area, and increased cup-to-disc ratio. There was diffuse thinning of the RNFL in all four quadrants (#3170).

Conventional VEP latency did not reveal a significant difference between optic disc drusen group and control subjects, but multifocal VEP (mfVEP) latency was greater in the drusen group, being abnormal in up to 70% of eyes (#3174).

The G-to-A transition at nucleotide 11778 in mitochondrial DNA in the gene specifying the NADH dehydrogenase subunit 4 (ND4) of complex I leads to Leber hereditary optic neuropathy (LHON). In a model for LHON, vitreal injection of wild-type human ND4 in rats containing the mutant human ND4 gene did not protect against retinal ganglion cell loss induced by mutant ND4. Wild-type ND4 injected 1 month before induction of optic neuropathy suppressed apoptosis by 33% and suppressed optic nerve head swelling at 6 months by 27%. Wild-type ND4 did not suppress optic neuropathy if injected at 6 months before induction of optic neuropathy. The lack of rescue was probably due to the dominant effect of the mutant human ND4 in the mouse (#3171). Some small-caliber unmyelinated efferent fibers were demonstrated in the optic nerves obtained at autopsy from patients with Leber hereditary optic neuropathy. These noradrenergic fibers were more numerous in the peripheral portion of the optic nerve (#2450).

In a case-control retrospective review of patients in whom traumatic optic neuropathy was diagnosed between January 2003 and May 2006, 30 of 38 patients with indirect traumatic optic neuropathy received megadoses of intravenous methylprednisolone (30 mg/kg loading dose followed by 5.4 mg/kg/h for 24-48 h), whereas eight patients were not treated. The corticosteroid-treated group on average had better visual acuity than the untreated group. These very preliminary results suggest that corticosteroid treatment may be beneficial in this form of traumatic optic neuropathy, but larger numbers are needed (#2479).

In a retrospective United Kingdom study involving 124 patients with giant cell arteritis (GCA), the authors found no difference in ischemic complications between patients with GCA who were treated with aspirin and those not so treated (#922).

**OPTIC NERVE IMAGING**

In 23 patients with MS who underwent RNFL and optic nerve head measurements using scanning laser polarimetry (GDx-VCC) and scanning laser ophthalmoscopy (HRT), significant differences between affected and fellow eyes were found for some GDx and mean RNFL HRT parameters. No significant correlation was observed between clinical assessment and imaging techniques. The results suggested that GDx and HRT measurements are an important tool in measuring axonal damage in MS (#908).

**VISUAL PATHWAYS**

A combination of self-assembly peptide nanofiber scaffold and chondroitinase ABC appears to create a more permissive environment in optic tract lesion repair, resulting in return of vision. The addition of self-assembly peptide Arg-Ala-Asp-Ala together with chondroitinase ABC increased the number of re-innervations after incisions in the optic tract of a hamster (#3168).

Intraventricular hemorrhage (IVH) is a major cause of adverse neurologic outcome after premature birth. VEP recordings were used to study visual cortex function in low-birth-weight infants with IVH. The study included 72 infants who demonstrated lower contrast and spatial frequency sweep parameters, a finding that may reflect neuronal loss by injury to germinal matrix, subclinical damage, or developmental delay (#3169).

Visual rehabilitation using Luebeck software in three patients with homonymous hemianopia (HH) resulted in an increase in the visual fields varying from 2 to 10. This resulted in an improved ability to read and walk (#952).

RGC function was studied in three patients with pathologic cupping of the optic nerve but normal vision and IOP who also underwent resection of non-secreting pituitary tumors. Before surgery, all six eyes showed pattern ERG (PERG) dysfunction with an average reduction of amplitude of 42.5% and average phase delay of 4.4%. After tumor resection, PERG amplitudes progressively recovered to normal. The authors hypothesized that there is blockage of retrograde axonal transport of neurotrophins in chiasmal compression. Interference in axonal flow was attributed to local ischemia of the optic chiasm in non-compressive
cases. A potential candidate for this hemodynamic perturbation is the vasoactive peptide endothelin-1 released by pituitary tumor (#928).

**IDIOPATHIC INTRACRANIAL PRESSURE (IIH, PSEUDOTUMOR CEREBRI)**

11-Hydroxysteroid dehydrogenase 1 (11BHSID1) has been previously identified in the ciliary body as an intraocular regulator of cortisol. A similar mechanism has been hypothesized for the control of cerebrospinal fluid (CSF) dynamics. Immunohistochemical analyses of postmortem human choroid plexus and arachnoid granulation tissue identified the presence of 11BHSID1. These results suggest that manipulating 11BHSID1 and CSF cortisol may have important therapeutic implications in regulating CSF dynamics and possibly intracranial pressure (ICP) (#927).

Inflammatory and adiposity-related cytokine profiles were studied using serum and CSF samples from patients with IIH and others undergoing lumbar puncture. Higher levels of serum and CSF leptin and lower levels of adiponectin were detected in patients with IIH than in other groups, suggesting a novel abnormality of the adipokine profile in IIH (#926).

A retrospective study of 110 patients with IIH showed that about 25% had an identifiable cerebral venous thrombosis detected by brain MRI (35.7%) and magnetic resonance venogram (MRV) (82%) and also had coagulopathies. The authors suggested that evaluation of a coagulopathy is mandatory in these patients and that they should not be classified as having IIH unless such studies are normal (#925). In a prospective study, CSF and serum were obtained from six patients with IIH and six control subjects to analyze for retinoic acid, retinol, retinyl esters, retinol-binding protein, and transthyretin, a transport protein for vitamin A. There was an increase in retinoic acid levels in normal (#925). In a prospective study, CSF and serum were obtained from six patients with IIH and six control subjects to analyze for retinoic acid, retinol, retinyl esters, retinol-binding protein, and transthyretin, a transport protein for vitamin A. There was an increase in retinoic acid levels in normal (#925).

**THYROID EYE DISEASE**

A session dedicated to thyroid-associated orbitopathy (TAO) focused on new directions for unifying basic and clinical science. Orbital fibroblasts in patients with Graves disease have been shown to be different from fibroblasts elsewhere in the body. Insulin growth factor (IGF-1) and interleukin-1 play important roles in the regulation of fibroblast proliferation and the inflammatory components of thyroid orbitopathy. Potential targets for treatment of Graves orbitopathy include antibodies to the IGF-1 receptor and cytokine antagonists. Several immunologic and hyperthyroid animal models of Graves disease (including mutants) were discussed, and the tree shrew was thought to be an appropriate model as it is a primate with a well-formed orbital cavity (#359). In an in vitro study, mouse extraocular muscles (EOMs) cultured with the addition of thyroid hormone (T3) demonstrated an increased level of caspase 8 and 3 activity compared with control EOMs. The results suggested that T3-induced hyperthyroidism in cultured EOMs is associated with apoptosis involving mitochondria and caspase pathways (#5276). In another in vivo hyperthyroid mouse model, the EOMs demonstrated an increase in myofibril thickness and mitochondrial density. This study highlighted the role of confocal scanning laser microscopy in the quantitative assessment of EOM changes and showed that it was comparable to the more time-consuming light and electron microscopy (#5626). Hypothyroid rats were used in an experimental study to evaluate the effect of thyroid hormone on the expression of thyroid hormone receptor-1 (TRb1) on the lacrimal gland. The authors concluded that the lacrimal gland expresses TRb1 and that hypothyroidism induces a higher expression of this receptor, confirming the fact that the lacrimal gland is a target organ for thyroid hormone and suggesting a mechanism for dry eyes in hypothyroidism (#416).

**PUPILS**

In a study of relative afferent pupillary defects (RAPDs) in amblyopia, horizontal pupil diameters and amplitude of contractions were studied in 12 patients with unilateral amblyopia (from ametropia or strabismus) using binocular infrared pupillography. Only one patient with moderate amblyopia was found to have an RAPD in the amblyopic eye, suggesting that only a small percentage of patients with unilateral amblyopia have a RAPD (#4878). Pupillary responses (amplitude, latency, constriction, and dilation velocity) to a graded light source over a standard ambient background were evaluated in 14 patients with RAPD to quantify and compare the asymmetry of the pupil reflex in ischemic to various other optic neuropathies. The authors found that the abnormally reacting pupil caused by ischemic optic neuropathy showed a slower maximum and mean constriction velocity and concluded that the comparison of the difference in amplitude constriction might distinguish the RAPD seen in ischemic versus other etiologies of RAPD (#5538).

Pupil contractions in response to chromatic stimuli (red and blue light) as a function of brightness were studied.
in 13 patients with photoreceptor disease (retinitis pigmentosa and rod-cone dystrophy) to differentiate the photoreceptor-mediated pupil responses from those of melanopsin-containing retinal ganglion cells. The diseased eyes demonstrated a relative decrease in the transient pupil response at low and medium intensities to both red and blue light stimuli. They also found that pupil dilation after a 10-second light exposure was slower after blue light than after red light stimulation. Thus, in eyes with photoreceptor disease, there is a relative decrease in the transient pupil response, indicating that the initial component of pupil contraction is mediated by photoreceptors in humans. The rapid pupil dilation after termination of light stimulation is probably mediated by a light-off signal from photoreceptors, which inhibits sustained firing on the pupil light reflex by the melanopsin-containing retinal ganglion cells. This study clearly demonstrates that patients with photoreceptor disease have abnormal transient and sustained pupil contractions that correlate with the physiologic response properties of melanopsin-containing retinal ganglion cells (#5535).

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The 59th Annual Meeting of the American Academy of Neurology highlighted breakthrough research on the most critical issues facing neurologists. More than 1,500 poster and platform presentations covering the spectrum of neurology were presented. We have summarized material of interest to neuro-ophthalmologists.

RETINOVASCULAR DISEASE

The results of local intra-arterial thrombolysis for CRAO with tissue plasminogen activator (tPA) in the ophthalmic artery were reported. All patients received “conventional therapy” with paracentesis and oxygen/carbon dioxide rebreathing with or without tPA. In the 21 patients receiving tPA, the visual acuity outcome was better than without tPA. Comparing treated and untreated patients at 24 hours: one Snellen line improvement in 71% vs 10%, 3 lines in 33% vs 5%, and final visual acuity better than 20/200 in 43% vs 14%. Although the results are encouraging, this study was not randomized and the average latency from onset of visual loss to treatment with tPA was 3 hours compared with 23 hours for those receiving “conventional therapy” (Lee AW, Baltimore, MD, S07.001).

TRANSIENT ISCHEMIC EVENTS

Thirty eight patients with transient global amnesia (TGA) underwent MRI scans with diffusion-weighted imaging (DWI). Ten were studied on an MRI with a 1.5 Tesla (T) magnet and 28 were studied on a 3.0 T magnet. Vascular risk factors were present in 17 patients and 14 episodes were triggered after emotional upsets. Among the 28 patients studied with 3.0 T, 29% showed unilateral or bilateral acute ischemic lesions of the hippocampus. None of the 10 patients studied with 1.5 T showed lesions. The authors appropriately concluded that high Tesla MRI may be helpful in detecting subtle ischemic changes in TGA (Lee SY, Seoul, Korea, P02.094).

A study focused on atypical clinical presentations of transient ischemic attacks (TIAs) had an interesting tangential finding. Of 395 TIA patients, 110 (29%) had abnormalities on DWI MRI, demonstrating that in many patients with TIA symptoms, there is some tissue infarction (Hakan A, Boston, MA, P01.097).

The effect of hospital admission on stroke risk following TIA in 552 patients was presented. Cumulative stroke risk at 30 days was lower (1.9%) in the group admitted (n = 381) than in the group not admitted (1.9%) (P = 0.002). These data suggest that the early risk of stroke is lower after TIA in those hospitalized than in those discharged from the emergency room (Poisson SN, Ann Arbor, MI, S24.001).

Pontine infarction may be lacunar or territorial (involving the entire territory of a penetrating artery). A study was designed to test the hypothesis that basilar artery abnormalities and certain vascular risk factors could determine which type of infarct had occurred. Among patients with lacunar infarcts (n = 12), there was no basilar stenosis and 75% had diabetes mellitus (DM). Among the patients (n = 13) with territorial pontine infarcts, 67% had basilar stenosis and only 31% had DM. These findings support the hypothesis that lacunar pontine infarct is associated with DM and territorial pontine infarct is associated with basilar stenosis. (Royter V, Los Angeles, CA, P01.109).

A case-control study was designed to determine if cardiovascular risk factors increase the risk of thromboembolic (TE) events during intravenous immunoglobulin (IVIg) infusions. Nineteen cases with TE events associated with IVIg infusions were compared with an age-matched control group without TE events. No single cardiovascular risk factor was associated with TE events, but the TE risk was elevated when 2 or more cardiovascular risk factors were present (odds ratio = 1.39). This trend became statistically significant when 4 or more vascular risk factors (odds ratio = 10.50, 95% CI: 1.91, 57.58) were present. This study suggests that clinicians who prescribe IVIg should carefully consider the risk of stroke and myocardial infarction in elderly patients with multiple cardiovascular risk factors (Caress J, Winston-Salem, NC, P08.122).

There is a growing use of transcranial Doppler (TCD) to screen patients with stroke or migraine for intracardiac right-to-left shunt (IRLS). A retrospective study compared the diagnostic utility and reliability of various provocative maneuvers for the detection of IRLS using TCD. Among
316 patients who had undergone TCD and transesophageal echocardiography (TEE), 125 (39%) had IRLS. Of these, 103 (82%) had a positive TCD study with cough and 107 (89%) with valsalva; 123 (99%) had a positive study with either cough or valsalva, and 69 (55%) had a positive study at rest. Only 63 patients (50%) had a positive study at rest, and after cough and valsalva. This study suggested that TCD could be useful to detect IRLS, especially with provocative maneuvers (Selim M, Boston, MA, P08.117).

**STROKE PREVENTION**

The SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial found that 80 mg/day atorvastatin reduced the future risk of stroke and major cardiovascular events in patients with stroke or TIA within the prior 6 months. In a post-hoc analysis, the effects of 80 mg/day atorvastatin in patients with a history of carotid stenosis participating in the SPARCL trial were determined. Among the 4731 subjects with carotid stenosis, randomization to atorvastatin treatment was associated with a 34% reduction in stroke. Major cardiovascular events (cardiac death, fatal and non-fatal myocardial infarction, stroke and resuscitated cardiac arrest) were reduced by 36% and revascularization procedures were reduced by 50%, including a 54% reduction in carotid revascularization (Sillesen H, Paris, France, S34.005).

Low cholesterol level is a known risk factor for intracerebral hemorrhage (ICH), and statin use increased the risk of ICH in a recent randomized trial. A single-center prospective cohort study sought to determine if statin use affected 180-day outcome and risk of ICH recurrence in those who had suffered ICH. Of 483 subjects, 100 were taking a statin at the time of ICH (21%). Statin users and statin non-users had a similar unadjusted 180-day mortality (45% vs 53%) and 180-day independence rate (27% vs 30%). In multivariate models adjusted for ICH volume and other factors, statin use was associated with an increased 180-day survival (OR = 2.32, 95% CI 1.27-4.22, $P = 0.006$) and 180-day independence rate (OR = 1.95, 95% CI 1.00-3.83, $P = 0.05$). The study concluded that there was a mild but not significant increase in risk of ICH recurrence in statin users (FitzMaurice E, Brookline, MA, S48.006).

A retrospective study evaluated the effect of aspirin use on outcome in ischemic stroke patients undergoing acute endovascular procedures. Among 77 patients the rate of recanalization was not different in patients on aspirin ($P = 0.3$). There was not an increased risk of ICH among patients on aspirin ($P = 0.2$). This study suggested that use of aspirin is not associated with increased risk of ICH in patients with acute ischemic stroke who undergo endovascular procedures (Alexandros L, Newark, NJ, P06.107).

A study evaluated the safety of aggressive blood pressure control with nicardipine infusion prior to IV tPA for acute ischemic stroke. Retrospective chart review of 258 patients that received IV tPA was divided into three groups: no medication, labetalol, and nicardipine (with or without labetalol) before IV tPA. The results suggested that the use of nicardipine prior to IV tPA treatment is not associated with an increased rate of ICH. Aggressive management of blood pressure higher than 185/110 with a rapidly active agent such as nicardipine may increase the number of patients eligible for IV tPA (Martin-Schild S, League City, TX, S44.008).

**TREATMENT OF STROKE**

A study of a single-center 10-year experience in thrombolysis for stroke patients 80 years or older was presented. Age 80 years was independently and inversely associated with functional independence at hospital discharge ($P = 0.030$) but not with increased risk of ICH or in-hospital mortality. The authors suggested that very old stroke patients may have higher baseline stroke severity and poorer functional outcomes at discharge, but that these data should not be used to exclude older patients from thrombolysis based on age alone (Flaster M, Phoenix, AZ, P06.124).

A study was designed to compare the long-term results of treatment of symptomatic intracranial stenosis with primary angioplasty ($n = 25$) or stent placement ($n = 22$). The mean stenosis decreased from 72% ($\pm 21\%$) to 29% ($\pm 22\%$) in the angioplasty-treated group and from 71% ($\pm 10\%$) to 21% ($\pm 21\%$) in the stent-treated group. There was no difference in time to ipsilateral stroke, repeat procedure, or death. At 24 months, major ipsilateral stroke-free survival was 69% ($\pm$SE of 17%) for angioplasty and 84% ($\pm$SE of 9%) for stent. There was a suggestion of a higher adverse event rate (repeat procedure, stroke or death) in patients treated with primary angioplasty at 24 months (Qureshi A, Bloomfield, NJ, P07.126).

**CAROTID ARTERY STENTING**

A single-center prospective study of 127 patients was undertaken to determine the risk of carotid artery stenting (CAS) in patients with pre-occlusive lesions (>90% stenosis) or the “string sign” of severe narrowing distal to the stenosis. The incidence of stroke and vascular death was 6.3%. This study suggested that severe ICA stenosis can be safely treated with protected CAS but the presence of a string sign may be an angiographic predictor of peri-procedural complications (Mazighi, M, Paris, France, P07.127).

**CEREBRAL VENOUS THROMBOSIS**

In a group of 230 consecutive patients with cerebral venous thrombosis (CVT), 9 patients had isolated CVT of
the posterior fossa. All patients had subacute presentation—4 with cerebellar symptoms and 5 with symptoms of intracranial hypertension. Three cases were idiopathic, three associated with the puerperium, and one each with oral contraceptive use, anemia, and dehydration. CT was nonspecifically abnormal in 5 patients, showing cerebellar infarction with mass effect in 5 patients and hemorrhage in 2. MRI was abnormal in 8 of 9 patients who had the study, showing venous sinus thrombosis. One patient was diagnosed by autopsy. Two (22%) patients died in the acute stage, one patient was discharged in a vegetative state; functional outcome was favorable in 6 (67%) patients. Initial diagnosis (tumor, arterial stroke) was often incorrect (Ruiz-Sandoval JL, Queretaro, Mexico, P01.098).

A randomized study comparing the treatment of CVT with unfractionated heparin or low molecular weight heparin (LMWH) was presented. Thirty five patients received unfractionated heparin in a dose of 800–1000 U/hour in infusion form, maintaining aPTT in range of 1.5–2 times normal for a duration of 7–10 days and 40 patients received LMWH 200 anti X-a units/kg/day in 2 divided doses for 7–10 days. Oral anticoagulants were continued subsequently for 3–12 months, maintaining INR of 2-3. In the unfractionated heparin group at 90 days, complete recovery was observed in 29 cases, partial recovery of 3 cases, and death in 3 cases. In the LMWH group, complete recovery was observed in 34 patients, partial recovery in 3 patients, and death in 3 cases. The authors concluded that anticoagulation is safe in CVT, even with hemorrhagic infarcts, carrying a morbidity and mortality of less than 10%. LMWH was found to be more cost effective, having fewer side effects and no requirement for lab monitoring (Modi M, Chandigarh, India, P01.099).

**DURAL FISTULA**

A retrospective analysis of 27 consecutive dural carotid-cavernous fistula (DCCF) patients was performed to determine the efficacy of treatment by transvenous embolization. Orbital and neuro-ophthalmological symptoms were the most common clinical presentation at diagnosis (n = 25). Venous drainage of the fistula involved the ipsilateral superior ophthalmic vein in 24 patients, the contralateral cavernous sinus in 6, and a lepto-meningeal vein in 5 cases. Twenty patients received endovascular treatment either via a transvenous (n = 16) or a transarterial approach (n = 4). Complete occlusion of the fistula was obtained in 87% of patients treated by the transvenous approach and in 25% of patients treated by the transarterial approach. One cerebral hemorrhage occurred after transvenous embolization of a DCCF with lepto-meningeal drainage. On follow-up, all patients treated by the transarterial route remained asymptomatic whereas 71% of patients treated by the transvenous route were asymptomatic. Although the numbers are small, this study suggests that transvenous embolization may be a safe and effective endovascular approach in patients with DCCF (Theaudin M, Paris, France, P05.019).

**CEREBRAL ANEURYSM**

A study compared endovascular and surgical approaches for unruptured intracranial aneurysm from Nationwide Inpatient Survey (NIS) data. In a two-year period, there were 19,648 admissions for unruptured intracranial aneurysms. Surgical and endovascular treatment was performed in 7,543 and 380 patient admissions, respectively. There was a trend for a larger proportion of patients aged 65 years or greater to be treated with endovascular treatment (P = 0.06). The length of hospitalization was shorter in patients treated with endovascular treatment (6 ± 0.5 versus 7 ± 0.2, P = 0.009). There was a trend toward a higher rate of discharge home (rather than to a long term medical care facility) for patients treated with endovascular treatment (85% vs 76%, P = 0.08). Endovascular treatment maybe associated with shorter length of hospitalization and higher rates of discharge to home (Divani A, Newark, NJ, P05.036).

**LEBER HEREDITARY OPTIC NEUROPATHY**

A study sought to determine if an increase in mitochondrial DNA copy number is a compensatory strategy in Leber hereditary optic neuropathy (LHON) in 35 patients, 57 unaffected carriers of LHON families with the 11778/ND4 mutation, and spouses of patients and carriers, who served as controls. Patients had a significant increase in mtDNA content per cell compared to controls but not as much of an increase as in unaffected carriers. These results suggest that increasing mtDNA may be a strategy of protection and may be successful in unaffected mutation carriers (Carelli V, Bologna, Italy, S07.002).

**NONARTERITIC ISCHEMIC OPTIC NEUROPATHY**

A retrospective review found that 23% of 727 consecutive patients with nonarteritic ischemic optic neuropathy (NAION) were affected when they were below the age of 50 years. Similar risk factors to older patients were found, but there was a relatively high risk of involvement of the fellow eye at 41% after a mean duration of 12 months. Only 6% had ipsilateral recurrence. Hypertension was found in 35%, DM in 21%, smoking in 29%, hypercholesterolemia in 20%, and small cup/disc ratio in 84%. Visual function was better in the younger group than the older group (Bruce B, Atlanta, GA, P01.138).
INFLIXIMAB AND OPTIC NEUROPATHY

A 79-year-old woman presented with blurred vision and decreased color perception and had finger counting at 2 feet OD and 20/50 OS, impaired color perception, right inferior quadrantanopia, and extensor plantar responses. Brain MRI revealed multi-focal, cystic-appearing, peripherally enhancing lesions involving both occipito-parietal and temporal lobes. The optic nerves showed increased T2 signal and mild enhancement bilaterally. CSF exam was normal except for slightly elevated myelin basic protein level (2.7 ng/mL). She underwent stereotactic brain biopsy of an occipital lesion. The pathology showed a non-neoplastic active inflammatory destructive white matter process with demyelination. In-situ hybridization for JC virus DNA was negative. Infliximab was suggested as the cause (Halker RB, Rochester, MN, P06.078).

MULTIPLE SCLEROSIS

The 15-year data from the Optic Neuritis Treatment Trial were reported. The most predictive feature for the subsequent development of clinically definite multiple sclerosis (CDMS) remained the brain MRI. In contrast to the 10-year data, where patients were stratified into 0 vs 1 or more intracranial white matter lesions, the 15-year data showed increasing risk with an increase in the number of lesions. The patients without MRI lesions had a 23% CDMS conversion rate, those with one or two lesions had a 56% CDMS conversion rate, those with 3 to 6 lesions had a 71% CDMS conversion rate, and those with more than 6 lesions had a 74% CDMS conversion rate (Eggerberger E, East Lansing, MI, LP50.001).

A study was done to evaluate the 2 different McDonald criteria for dissemination in space in patients with demyelinating “clinically isolated syndromes” (CIS) to see which is better in predicting subsequent conversion to CDMS. The first criterion was MRI lesions alone and the second was MRI lesions and positive oligoclonal bands (OCB) in the cerebrospinal fluid (CSF). Fifty-eight patients with CIS were prospectively studied with follow-up at 5 years. The sensitivity of MRI lesions alone was 73.53%, specificity was 87.50%, and accuracy was 79.31%. The presence of at least two MRI lesions plus oligoclonal bands yielded a sensitivity of 94.29%, a specificity of 95.65, and an accuracy of 94.82%. The presence of OCB plus two MRI lesions is highly accurate in predicting CIS conversion to CDMS. MRI criteria alone have a high specificity but less sensitivity and accuracy than MRI plus OCB (Alvarez-Cermeno JC, Madrid, Spain, S22.004).

In a 20-year follow up study on 85 patients with CIS, MS developed in 55 (64%), in 88% with an abnormal baseline MRI scan and in 19% with a normal baseline MRI scan. Among those who developed MS, 22 had developed the secondary progressive (SP) form and 33 the relapsing-remitting (RR) form at follow-up. T2 lesion volume at baseline and at 20 years correlated moderately with EDSS ($P < 0.003$). The estimated rate of lesion growth was 2.24 cm$^3$ per year in SPMS and 0.79 cm$^3$ per year in RRMS. The difference of 1.45 cm$^3$ per year was highly significant ($P < 0.001$). The study suggested that lesion load continues to increase for at least 20 years in relapse-onset MS and that the rate of lesion growth is higher in SPMS than in RRMS (Fisniku LK, London, United Kingdom, S42.004).

The outcome of patients with subclinical MRI “demyelinating lesions” was the subject of 2 reports. A group of 7 women and 3 men with MRI white matter lesions discovered during evaluation of headaches were followed for a mean of 66.4 ± 41.6 months after the initial MRI. Using the McDonald criteria, 50% of the patients converted to MS over a mean follow-up period of 48.2 ± 30.3 months. Mean age at initial MRI tended to be older for converters (44.8 ± 15.6) than non-converters (26.0 ± 7.1) (Siva A, Istanbul, Turkey, P04.069).

A study reported the 5-year MRI and clinical follow-up in 30 patients with subclinical MRI demyelinating lesions found during investigation of headache (14), migraine (6), cranio­cerebral trauma (3), depression (3), endocrinopathies (2), epilepsy (1), and cognitive deterioration (1). The mean time for second brain MRI was 6 months. At that time, 80% had developed MRI evidence of dissemination of disease in time and space. Eleven patients developed a clinical episode of demyelination, consisting of optic neuritis in 5, brainstem dysfunction in 3, sensory symptoms in 2, and cognitive deterioration in 1. The mean time between the first brain MRI and CIS was 2.3 years (0.8-5) (Lebrun C, Nice, France, P04.082). These two studies demonstrate that coincidentally finding MS lesions on MRI carries risk of subsequent CDMS in a manner similar to having a CIS.

Several analyses of the association of MS with other immune diseases were reported. A study of 31044 subjects came from the Sample Adult file of the 2002 National Health Interview Survey (NHIS). The MS population ($N = 89$) had an increased prevalence of asthma (26.5% vs 10.6%, $P < 0.0001$), chronic bronchitis (11.2% vs 4.4%, $P = 0.004$), inflammatory bowel disease (18.7% vs 5.5%, $P < 0.0001$), thyroid disease (13.1% vs 6.9%, $P = 0.08$), allergies to food/odor (22.7% vs 6.9%, $P < 0.0001$), allergies to medication (20.6% vs 13.0%, $P = 0.06$), and skin problems (14.3% vs 8.7%, $P = 0.07$) compared to the general population. Subjects were at higher risk of having MS if they had asthma (OR = 3.1, 95% CI 1.8-5.3), chronic bronchitis (OR = 2.7, 95% CI 1.4-5.4), inflammatory bowel disease (OR = 4.0, 95% CI 2.7-8.7), thyroid disease (OR = 2.0, 95% CI 0.9-4.5), allergies to food/odor (OR = 4.0,
95% CI 2.1–7.6), allergies to medication (OR = 1.7, 1.0–3.1), and skin disease (OR = 1.8, 95% CI 1.0–3.2). Age and sex-adjusted logistic regression showed that the presence of at least one of these immune-mediated conditions increased the odds of having MS by a factor of 2.8 (95% CI 1.8–4.4, \( P < 0.0001 \)). There was an exponential relationship between the number of simultaneously diagnosed immune-mediated conditions and the odds of having MS (Finkielstein J, Baltimore, MD, P04.067).

Prior small epidemiologic studies have suggested that psoriasis and rheumatoid arthritis (RA) are associated with an increased risk of MS. A case-control study using data from the General Practice Research Database, containing the electronic medical records of about 5% of the UK population, identified 4423 cases with demyelinating conditions (73% MS, 21% optic neuritis, 3% transverse myelitis) and used 22,115 controls. Psoriasis was not associated with an increased risk of demyelination and there was an inverse association with RA (Mines D, Collegeville, PA, P04.081).

Three OCT studies produced results that support the use of RNFL thickness as an outcome measure in clinical trials of neuroprotective or neuro-reparative drugs in MS. One OCT study of MS patients found that RNFL thinning correlates with brain atrophy (Gordon-Lipkin E, Baltimore, MD P02.044). Another OCT study found that RNFL thickness was strongly associated with brain volume and was inversely associated with disability (Grazioli E, Buffalo NY, P02.050). A third study looking at inter-rater and cross-center reproducibility of OCT found that there is good reproducibility in both (Cettomai D, Baltimore, MD, P02.051).

Improvement in motor function has been reported in MS patients treated with fampridine (4-aminopyridine). A Phase 3 multi-center trial of oral fampridine found had a higher proportion of responders in the treated than in the placebo group (34.8% vs 8.3%; \( P < 0.001 \)), with improvement in walking speed (Goodman A, Rochester, NY, S32.003).

A comparative study of intravenous mitoxantrone (MTX) and cyclophosphamide (CTX) in MS was reported. Seventy-five patients received MTX (31 RR, 44 secondary progressive) and 78 CTX (15 RR, 63 SP). There was no significant difference in time to first relapse but time to progression was slightly shorter in MTX than in CTX patients. Active MRI scans were reduced by 69% in MTX patients and 63% in CTX patients (\( P = 0.10 \)). Side effects led to discontinuation of therapy in a significantly higher proportion of CTX patients. CTX may represent a therapeutic alternative to MTX for very active/progressive MS (Zipoli V, Florence, Italy, P06.076).

Combining intramuscular interferon beta 1a (IM IFN β-1a) with immunosuppressive agents might theoretically improve treatment efficacy. A double-blind, placebo-controlled study compared the efficacy of IM IFN β-1a plus azathioprine (AZA) alone or with prednisone, with that of IM IFN β-1a monotherapy. There were no significant differences in disability progression among the treatment groups at 2 and 5 years (Havrdova E, Buffalo, NY, P06.089).

A study compared the side effects of high doses of intravenous and oral methylprednisolone (MP) in MS. Patients received 1 g/day IV MP for 3 to 5 days (58 courses) or 1 g IV MP the first day and 1 g orally/day for 2 days (59 courses). The frequency of side effects was similar in the 2 protocols and included metallic taste (74% vs 78%), headache (34.5% vs 45.8%), digestive manifestations (27.6% vs 34%), flushes (46.6% vs 40.7%), cutaneous eruption (8.6% vs 13.6%), insomnia (51.7% vs 42.4%), psychiatric manifestations (36.2% vs 47.5%), infections (5.4% vs 5.1%), and palpitations (19% vs 30.5%). One patient had a slight hypokalemia. Most symptoms disappeared rapidly after the last pulse of MP. This study suggests that the side effects of high doses of MP did not differ when the medication was given IV or orally (Le Page E, Rennes, France, P06.100).

BECOME is a randomized, prospective study comparing the efficacy by MRI parameters of standard doses of Betaseron (interferon [IFN] β-1b) (Bayer HealthCare Pharmaceuticals, Wayne, NJ) and Copaxone [glatiramer acetate (GA)] (Teva Pharmaceutical Industries Ltd., Peta- tikva, Israel) in patients with relapsing MS over 2 years. A total of 75 patients were randomized to receive either IFN β-1b (36 patients) or GA (39 patients). Using 3.0 T MRI, no difference was observed in the development of new lesions between the two groups (Lincoln JA, Valencia, Spain, S42.005).

**NEUROMYELITIS OPTICA**

A study of neuromyelitis optica (NMO) IgG antibody (Ab) in 130 patients with active RR MS found that none of the patients had measurable NMO antibody. The rationale for the study was that prior reports comparing NMO and MS patients may have been biased by including stable inactive MS patients and that NMO Ab might be related to disease activity as an epiphenomenon of active inflammation. The patients in this study all had at least one relapse in the past year, were off immunomodulatory agents for at least 2 months, and were being enrolled in a rituximab trial. These results support the high degree of specificity of NMO Ab for NMO (Smith C, San Francisco, CA, P01.039).

A study reported the prevalence of NMO Ab in 20 patients from 2 medical centers who met the 1999 diagnostic criteria for NMO. Only 6 patients (30%) had the Ab. Time from symptom onset was much greater in those with the Ab (13.5 years) than in those without Ab (5.5 years). Extensive spinal cord involvement was seen in 50%
of those with Ab and in no one without Ab. This small series raises the possibility that NMO positivity may relate to duration of disease and extent of spinal cord involvement (Glisson CC, Philadelphia, PA, P01.145).

There was a study of NMO Ab prevalence in patients with NMO, MS, and controls with or without other immune diseases. NMO Ab was found in 21/37 patients with NMO and in 6/6 patients with isolated longitudinally extensive transverse myelitis (LETM), who are considered to be at high risk for NMO. By contrast, Ab was present in only 4/144 patients with MS and was absent in patients with systemic autoimmune diseases (0/45) and in healthy controls (0/29), corresponding to a sensitivity and specificity of 56.8% and 98.3% for NMO. These findings suggest that testing for NMO Ab enables a reliable distinction to be made between NMO and MS and between NMO and other autoimmune diseases affecting the CNS (Jarius S, Oxford, United Kingdom, P04.060).

A study was designed to test the pathogenicity of the anti-aquaporin-4 antibodies in a rat model. Adult rats were immunized with peptides corresponding to the extracellular domains of the aquaporin-4 water channel. When anti-aquaporin-4 antibody titers reached or surpassed titers observed in patients with NMO, the rats were injected intraperitoneally with a pro-inflammatory lipopolysaccharide (LPS) that transiently increased the permeability of the blood-brain-barrier to antibodies, including the anti-aquaporin-4 antibodies. Immunized rats injected with LPS developed weakness and motor incoordination in all four extremities, limiting their ability to walk over a grid. Prior to injection of LPS, the rats had no motor dysfunction and unimmunized rats injected with LPS did not develop weakness. This study provides hope for a preliminary rat model of NMO by pro-inflammatory LPS injection in the setting of immunization against the aquaporin-4 water channel (Levy M, Baltimore, MD, P04.061).

A retrospective analysis of rituximab treatment of 24 cases of NMO was presented. Two patients died of intercurrent infections 10 and 12 months after last rituximab infusion. The posttreatment relapse rate was significantly lower than the pretreatment relapse rate. EDSS scores of 91% of patients stabilized or improved. Infusion-related transient side effects occurred in 25% of patients and were not dose-limiting. Rituximab was associated with a reduced number of attacks and improved or stable disability but the occurrence of two deaths raises safety concerns (Jacob A, Port Jefferson, NY, S32.002).

A study of patients with NMO or LETM was designed to determine the overlap with Sjögren syndrome. Seventeen patients diagnosed with NMO, isolated LETM, or recurrent optic neuritis had extensive serological workups for autoimmunity. Lip biopsies were performed for diagnosis of Sjögren syndrome. Four out of 6 patients with clinical NMO had a strongly positive lip biopsy consistent with Sjögren syndrome. Three out of 4 patients with high NMO-IgG titers had a positive lip biopsy. Five out of 5 patients with LETM had a positive lip biopsy. No patients with recurrent optic neuritis had a positive lip biopsy. Only 2/10 patients with a positive lip biopsy had elevated SSA or SSB. The authors concluded that a high percentage of patients with NMO or LETM have features of Sjögren syndrome (Javed A, Oak Park, IL, P04.058).

Fundoscopic examinations, fundus photography, and Stratus OCT were performed on 10 NMO patients and 13 MS patients with a history of ON. In contrast to MS, NMO patients often had narrowed arterioles that extended far into the retinal periphery and appeared to have thickened vessel walls (0/26 MS eyes, 15/20 NMO eyes, \(P < 0.0001\)), suggesting vascular pathology in NMO. The average RNFL was thinner in NMO patients (67.9 microns in NMO compared to 90.4 microns in MS, \(P < 0.017\)). Rather than being concentrated in the maculopapular bundle, thinning of the RNFL in NMO appeared to be more diffuse, involving the arcuate bundles and nasal portion of the nerve fiber layer. Distinct vascular changes on fundoscopic examination and markedly reduced RNFL thickness on OCT may eventually assist in distinguishing NMO from MS (Green A, San Francisco, CA, S52.004).

**IDIOPATHIC INTRACRANIAL HYPERTENSION (IIH)**

A study of idiopathic intracranial hypertension (IIH) in African Americans included 263 white patients and 203 African American patients. Obesity, hypertension, anemia, and sleep apnea were more common in the African American patients. Visual acuity initially and at follow-up was worse in this group. Humphrey visual fields were not different at presentation but were worse at follow-up in the African Americans. The relative risk of blindness for African Americans was 3.2 for one eye and 4.8 for blindness in both eyes. The opening pressure averaged 40 cm H\(_2\)O in African Americans and 34 cm H\(_2\)O in whites. This pressure difference was proposed as one feature that might underlie the clinical differences. This study suggests that IIH in African Americans is a relatively aggressive disease (Bruce B, Atlanta, GA, S07.003).

**HEMISPATIAL NEGLECT**

A study of hemispatial neglect in the first 2 months following cerebellar stroke in 28 patients was presented. Based on the hypothesis that cognitive deficits occur due to disruption of reciprocal cerebrocerebellar connections, the neglect would be expected to be on the same side as the lesion. However, among the 29% who had neglect, it was equally ipsilesional and contralesional. In 12 patients who
had SPECT perfusion scans, no correlation of perfusion defects with side of neglect was seen. The authors speculate that vestibular disruption may have a role in this condition (Kim EJ, San Francisco, CA, P01.005).

**VISUAL RESTORATION THERAPY IN HOMONYMOUS HEMIANOPIA**

A report of the role of visual restoration therapy (VRT) in visual field improvement in 118 patients with homonymous hemianopia was presented. Visual fields were measured with suprathreshold 43 × 32° high resolution campimetry pretreatment and monthly for 6 months. Among 118 patients, the mean absolute improvement in stimuli detection was 12.3%. Improvements of >3% were found in 85 patients (72.0%). Improvement did not correlate with age, duration of lesion, or whether the hemianopia was complete or partial (Romano JG, Miami, FL, S37.005).

**THIRD CRANIAL NERVE PALSY**

A review of publications related to evaluation of third nerve palsy with digital subtraction angiography (DSA) and computerized tomographic angiography (CTA) was presented. The author’s conclusion was that CTA should be performed except in patients with no pupillary dysfunction and complete external dysfunction. If CTA is negative, DSA is indicated only if there is pupil dysfunction and complete EOM and lid dysfunction in men younger than 50 years. Patients with normal pupils and partial external dysfunction do not need DSA except if there is superior division palsy or the patient is less than 50 years old (Fletcher WA, Calgary, AB, Canada, POL 154).

**MYASTHENIA GRAVIS**

Studies of patients with muscle-specific tyrosine kinase (MuSK) antibody-positive myasthenia gravis (MMG) showed some differences in response to therapy as compared to those with acetylcholine receptor (AChR) antibody-positive MG.

A study reported that Anti-MUSK antibodies were found in 31 of 67 patients with generalized MG treated with weekly methotrexate injections (25–50 mg) showed that 87% improved. Only 1 patient developed a side effect of elevated hepatic enzymes which reversed on discontinuation of the drug. This study suggests that methotrexate could be an alternative drug for treatment of refractory MG (Abdou AM, Alexandria, Egypt, P07.035).

**NYSTAGMUS**

In 117 patients with downbeat nystagmus (DBN), 62% had an identifiable cause, including cerebellar degeneration (21%), stroke (9%), and cervico-medullary junction malformations (7%). Two novel causes reported were episodic ataxia type 2 and vestibular migraine (Wagner JN, Munich, Germany, S07.005).

A randomized, double-masked, placebo-controlled trial of memantine or gabapentin in 48 patients with congenital nystagmus (idiopathic or associated with afferent pathway disease) was reported. Outcome measures were visual acuity, nystagmus intensity, and foveation time, and subjective questionnaires about visual and social function. Memantine and gabapentin showed a significant benefit over placebo (P = 0.004). Patients with afferent disease had little improvement in visual acuity but eye movement recordings did show some improvement. There was no significant difference between the effects of gabapentin and memantine. This well-designed small study demonstrates that gabapentin and memantine may benefit patients with
congenital nystagmus (Gottlob I, Leicestershire, UK, S07.006).

Benign paroxysmal positional vertigo (BPPV) is often cured by canal repositioning maneuvers. A study of the recurrence rate in BPPV patients with either posterior canal BPPV (352 patients) or horizontal canal BPPV (270 patients) was presented. With horizontal canal BPPV, the recurrence rate was 4.1% at 30 days, 19% at one year, 25% at two years, 27% at three years, and 32% at six years. With posterior BPPV, the rates were 3.4% at 30 days, 21.9% at one year, and 40.8% at six years. The study shows that even after successful treatment, BPPV recurs in a significant proportion of patients and increasingly over time (Kang J, Seoul, Republic of Korea, P01.151).

**MOVEMENT DISORDERS**

In a study of visual function in Parkinson disease (PD), the NEI-VF25-QOL score was reduced to 79 compared to 97 for controls. Low-contrast visual acuity and contrast sensitivity best distinguished between PD patients and controls (Ko MW, Philadelphia, PA, P01.137).

Two pathologic studies of progressive supranuclear palsy (PSP) demonstrated the challenges in diagnosing the disease. The clinical presentations and antemortem diagnoses were reviewed in 19 pathologically-proven cases of PSP. Clinically, 11 had had findings typical of PSP, two had had findings typical of PD, two had had findings typical of Alzheimer, two had had findings typical of Alzheimer and Lewy body dementia. The correct clinical diagnosis of PSP was made in only four patients. This study shows that the diagnosis of PSP is often missed antemortem in favor of other PD-like illnesses (Evidente VG, Scottsdale, AZ, P02.021).

PSP is considered to have 2 clinical phenotypes: classic PSP (Richardson syndrome) and PSP-parkinsonism. Among 21 consecutive patients proven pathologically to have PSP, 24% had been clinically characterized as having PSP-parkinsonism and 67% as having Richardson syndrome. Two patients had progressive aphasia, dressing apraxia, and an alien hand, which the presenters classified as a third clinical phenotype that they called “PSP-cortical dysfunction.” The post-diagnosis lifespan of the patients with PSP-parkinsonism was significantly longer (11.6 years) than that of the patients with Richardson syndrome (6.4 years) or those with those with PSP-cortical dysfunction (5 years). Men predominated only in the Richardson syndrome cases. The PSP-parkinsonism patients did not have supranuclear palsy or falling early in the disease course and could not be easily differentiated from PD. This study, like the study described above, points out the phenotypic variance of pathologic PSP (Kanazawa N, Niigata, Japan, P02.023).

**HEADACHE**

The efficacy of prophylactic botulinum toxin A (BTX-A) injections in preventing migraine headache attacks is controversial. Two studies tested BTX-A in the treatment of migraine. In a study to determine whether the presence of cutaneous allodynia (CA) is correlated with better response, 70 patients with episodic migraine were enrolled in an 8 month randomized, double-blind, placebo-controlled, crossover study. Patients were divided according to presence of CA (30 with and 40 without CA) and assessed by quantitative sensory testing (QST). Both groups were injected at baseline and after 4 months with BTX-A (total dose 80 U) and/or placebo (saline). Only the patients with CA reported significant reduction \( P < 0.01 \) of migraine frequency and number of headache days following BTX-A treatment. This study suggests that CA could be a predictive factor for responders to BTX-A prophylactic therapy in migraine (Relja M, Zagreb, Croatia, S25.005).

A study examined the efficacy, safety, and satisfaction with BTX-A treatment in 61 migraine patients previously failing prophylaxis due to compliance issues. This was a randomized, double-blind, single-center, placebo-controlled study (months 1–3) with a subsequent cross-over to open-label BTX-A treatment (months 4–6) for placebo-treated patients. The number of headache days and headache frequency decreased from baseline at months 2, 5, and 6 in BTX-A-treated patients but at no time point for placebo-treated patients. This study suggests that BTX-A may be a useful treatment option for migraine patients demonstrating low compliance with other prophylactic regimens (Schreiber CP, Springfield, MO, P08.004).

A study compared efficacy and safety profiles of topiramate and amitriptyline for migraine prophylaxis. Eligible subjects aged 18 years or less with episodic migraine were randomized to treatment with 50 mg topiramate twice a day (169 patients) or 100 mg at bedtime amitriptyline (157 patients) for 26 weeks. Topiramate resulted in statistically significant improvements in all three Migraine-Specific Quality-of-Life Questionnaire (MSQ) domains compared with amitriptyline. Improvements in the Quality of Life–Enjoyment and Satisfaction Questionnaire—Short Form (Q-LES-Q-SF) and Migraine Disability Assessment (MIDAS) were similar for both treatments. The most commonly reported adverse events were: topiramate–paresthesias (30%), fatigue (17%), somnolence (12%), hypesthesia (11.0%), nausea (10%); amitriptyline–dry mouth (36%), fatigue (24%), somnolence (18%), weight gain (14%), dizziness (11%). This study showed that topiramate was at least as effective as amitriptyline in reducing mean monthly migraine episode rates and that amitriptyline was more likely to cause weight gain (Dodick D, Scottsdale, AZ, P08.001).
PARTIAL EPILEPSY LOOKING LIKE HEMIFACIAL SPASM

A 58-year-old man had excessive blinking of the left eye and upper face that was continuous for months. He reported a similar bout of facial twitching 3 years prior to presentation that had spontaneously resolved after 3 months. On examination, the movements had a tonic and clonic component and substantially attenuated or disappeared during volitional tasks such as grimacing, tongue protrusion, and mouth opening. Video EEG showed frequent right frontotemporal epileptiform discharges associated with the left facial twitching. He experienced nearly complete resolution with 1,400 mg/day carbamazepine. This case report suggests that partial epilepsy can look like hemifacial spasm even if the abnormal movements disappear during voluntary motor tasks (Espay AJ, Cincinnati, OH, P04.056).

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Optic Nerve Disorders, 2nd Edition


Scope: This is the second edition of a monograph originally published by the American Academy of Ophthalmology (AAO) in 1996 as part of its Ophthalmic Monograph series. The original monograph covered anatomy, physiology, clinical testing, and clinical features of most optic neuropathies in 10 chapters and about 250 pages. It was edited by Lanning B. Kline, MD, a noted neuro-ophthalmologist (and now chair of ophthalmology at University of Alabama-Birmingham), who also wrote several chapters.

The AAO contracted to Oxford University Press to reissue these monographs under Oxford's banner and with the input of its experienced copyeditors. The second edition is not very different from the first except that many of the authors have changed. Dr. Kline remains as co-editor (and author) and is joined by Rod Foroozan, MD, who has co-authored two chapters. One of the authors from the previous edition (John Morrison, MD) is still featured, but the remaining authors have been replaced by Lawrence Buono, MD, Eugene Eng, MD, Lisa Hinckley, MD, John Kerrison, MD, Michael Siatkowski, MD, and Michael Vaphiades, DO. Each has done a creditable job.

Strengths: Anatomic features, physiologic principles, and clinical features are broadly yet succinctly covered. The prose is consistently clear and very readable, no doubt reflecting the skill of Catharine Carlin, Oxford's chief copyeditor on this volume. The illustrations, many carried over from the first edition, are a judicious mixture of colorful and beautifully rendered anatomic and schematic drawings, fundus photos, visual fields, brain imaging, and histopathologic pictures. The authors ably handle the critical clinical issues and provide up-to-date information, some of it drawn from clinical trials and much of it new in this edition. The references have also been updated. The authors are forthright about acknowledging when evidence does not support standard treatments (as in corticosteroids or optic canal decompression for indirect trauma to the optic nerve).

Weaknesses: The topic is narrow—optic neuropathy and only optic neuropathy.

Recommended Audience: The book is written for ophthalmologists (and perhaps neurologists), but will they be willing to purchase a volume with such narrow coverage?—perhaps, if it comes at a bargain price as part of a subscription for the entire monograph series.

Critical Appraisal: This is a tidy take on an important topic. For those who want "the short version," it is a fine choice. Neuro-ophthalmologists may not discover enough content, but if they are teaching this material, they should consider it a useful resource. At the very least, the anatomic and schematic illustrations are worth cribbing.

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How to Examine the Nervous System, 4th Edition


Scope: This is a 211-page single-author paperback book describing the technique of performing a general neurologic examination. The author is an erudite, well-respected neurologist, and it is clear that he has abundant enthusiasm for neurology and for teaching.

Some of the chapters are symptom-based (loss of vision, conjugate gaze deviation, ptosis), some are anatomically based (upper limb, lower limb), and some are based on neurologic function (reflexes, gait). This feature does not detract from the appeal of the text but may seem confusing to students. There is a surprisingly large amount of text devoted to the neuro-ophthalmic examination (7 chapters, 86 pages).

Strengths: The author's writing style is smooth and confident, based on years of neurologic practice and teaching. He achieves an excellent mixture of necessary attention to detail without an over-reliance on technique. Students of neurology at all levels of experience will benefit from the practical advice about interpreting physical findings. Because the formal neurologic examination has not changed substantially in many years, none of the information is outdated. Although specific diseases are not covered, the author skillfully integrates the clinical applications of each test.

Weaknesses: The organization of the chapters is non-intuitive: the upper limb and lower limb are discussed in chapters separate from the corticospinal system and sensation. Although the amount of attention to neuro-ophthalmology is welcome, it seems a little disproportionately, particularly when speech and station/gait/balance receive a combined total of 6 pages! More figures and
tables would be helpful. Although this book does not claim to be a neuroanatomy review, some diagrams would be helpful to better understand the basis of a physical finding.

**Recommended Audience:** This book serves well as a review of the neurologic examination. It is not detailed enough for neurology residents but would be excellent for ophthalmology residents, practicing ophthalmologists, internists, and neuro-opthalmologists wishing to reacquaint themselves with the complete neurologic examination.

**Critical Appraisal:** This is an extremely well-written primer on the neurologic examination. This would make a nice companion to a traditional neurology textbook.

**Human Brain Anatomy in Computerized Images, 2nd Edition**


**Scope:** This is a meticulously prepared brain atlas of the cortical and sulcal anatomy of more than 30 human living subjects using a voxel-rendering technique developed in the author's laboratory. This second edition offers entirely new images from new living subjects.

The stated goals of this work are to assist both clinicians and researchers in analyzing human neuroanatomic images and to serve as a teaching tool for students primarily learning about neuroanatomy through modern radiology images rather than through post-mortem specimens.

Unlike most anatomic atlases that are never actually "read" but are opened and quickly paged through when needed to look up relevant anatomy, this book requires some careful study before use. The first chapter must be digested to orient oneself to the organization of the sections and to understand the rationale behind the use of multiple subjects' brains rather than just one set of images.

In the opening pages of the second chapter one finds a gold mine of plainly stated information, summarizing all of the important sulcal and cortical landmarks of the brain. Color-coded three-dimensional (3D) renderings of a dolichocephalic (otherwise normal) brain follow. The sulci are identified and the gyri are labeled. There is a useful set of images with Brodmann's cytoarchitectonic regions superimposed on the gyri.

Chapters 3 and 4 depict the 3D surface rendering of normal brachycephalic brains to illustrate differences from the dolichocephalic brain in Chapter 2.

Chapter 5 presents a series of 26 normal, 3D-labeled brains in black and white, each viewed from 6 directions, allowing one to appreciate the variability between subjects.

Chapter 6, entitled “Quantifying Neuroanatomic Differences,” coauthored with John Allen and Joel Bruss, is a departure from the remainder of the atlas, reading more as a primer for quantifying brain structures using MRI and specialized software. There is also a summary of the literature on brain volumetric studies.

Chapters 7 through 9 comprise the bulk of the atlas, with over 500 pages of two-dimensional MRI black and white slices, 5 mm thick, from three different brains. "Non-brain structures" (scalp, orbits, bone, etc.) are removed from the images for labeling ease, an approach initially unsettling to those accustomed to viewing in vivo CT scans and MRIs.

**Strengths:** A major thrust here is the emphasis on the differences in sulcal and cortical anatomy between and within individuals and how the failure to recognize these differences will inevitably lead to errors in both clinical practice and research. Likewise, the lack of standardized radiology imaging planes of orientation is discussed as another source of anatomic confusion.

To those ends, the complete sets of brain images presented in three different axial angles, in three differently shaped heads (dolichocephalic, brachycephalic, and extreme brachycephalic) are particularly helpful for research and everyday clinical practice. This approach is really quite remarkable compared with the traditional neuroanatomical atlas practice of presenting one “standardized” set of images, perhaps even in multiple planes, but ignoring the frustratingly common problem of trying to locate a patient's lesion to a specific gyrus in the face of obvious neuroanatomical variations. Dr. Damasio's atlas tackles this problem "head on," giving the user multiple normal variations to scrutinize.

**Weaknesses:** The atlas is dedicated entirely to cerebral cortical and sulcal anatomy. A disappointing (but intentional) feature is the lack of labeling of any brainstem nuclei or white matter fiber tracks (beyond the corpus callosum and internal capsule). The lobules of the vermis are not named. With hundreds of pages and an initially confusing array of images, color-coded tabs on page edges marking the sections would have facilitated quick referencing.

**Recommended Audience:** Any physician or researcher who evaluates neuroanatomic images may rely on this atlas as a precise reference for gyral and sulcal localization and variations. The atlas should be an excellent source for interpreting functional MRI studies and for the preoperative localization of brain lesions. Students who are primarily
learning about neuroanatomy through MRI and CT will find
this a dependable teaching tool.

**Critical Appraisal:** Dr. Damasio has produced a painstak­
ingly comprehensive second edition of her atlas of human
brain anatomy. If readers absorb the first 2 chapters, they
will be rewarded with a thorough understanding of the
individual variability of the human brain.

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**Thieme Atlas of Anatomy: Head and Neuroanatomy**

Michael Schuenke, MD, PhD, Erik Schulte, MD, Udo
Schumacher, MD, et al. Thieme, Stuttgart, Germany,

**Scope:** This is the first English translation of the famous
Thieme Atlas published in German in 2006. It is one of
three atlases in a series. The others are entitled General
Anatomy and Musculoskeletal System and Neck and
Internal Organs. Like the other two atlases in the series,
this is a giant softcover book of over 400 pages and more
than 1,000 illustrations. The illustrations are drawings, but
unlike other anatomic atlases, the drawings are not limited
to anatomy. They include schematic diagrams that illustrate
physiology, histology, and clinical examination.

**Strengths:** The medical artists at work here are in­
comparable. The effect is breathtaking. You can inspect the
tissues from every conceivable angle and in various layers.
The anatomic renderings are matched with pictures of
clinical and physiologic phenomena to make this into
a complete teaching package. For example, the arterial
circulation of the brain is shown first from its origin in the
aortic arch, then from the skull base, then in relation to the
underside of the brain, from the convexity, with the frontal
operculum retracted, and from the interhemispheric fissure.
Then the arterial domains of each circumflex vessel are
shown anatomically and schematically together with the
common stroke syndromes.

**Weaknesses:** There are no weaknesses.

**Recommended Audience:** This book would be useful for
medical students, house officers, and practicing physicians.

**Critical Appraisal:** Over 100 years ago, Sir William
Osler’s person-to-person bedside approach became the
model for medical training in the United States in the 20th
century. But this “eminence”-based medical model is now
vying with the “evidence”-based model, particularly as we
invent increasing numbers of tests and therapeutic options
that force an emphasis on considering cost-benefit ratios.
An understanding of the importance of medical statistics,
the application of Bayes’ theorem, and probability equa­
tions will become an imperative part of all aspects of
medical care. This book makes a substantial contribution to
this trend.

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**Medical Decision Making**

Harold C. Sox, MD, Marshall A. Blatt, MD, Michael C.
Higgins, PhD, and Keith I. Marton, MD. American
1-930513-79-8, $39.95.

**Scope:** This is a rapid-fire introduction to the use of Bayes’
theorem in understanding, assessing, and selecting tests to
prove or disprove a diagnostic differential diagnosis and
therapeutic options. The book is divided into 11 chapters,
including the process of differential diagnosis, quantifying
uncertainty, use of Bayes’ theorem in analyzing new
information, and measuring the accuracy of clinical data.
The authors then go on to talk about valued decision
making and measuring the outcome of care. The last
sections move on to decision-making when outcomes have
several dimensions, selection and interpretation of diag­
nostic tests, bedside decision analysis, and cost-effective
analysis. The authors also include an appendix on test
characteristics and life tables. Each chapter is followed
by questions based on the material within the chapter,
requiring use of formulas and calculations.

**Strengths:** The authors have a proselytizing approach to
the importance of the cost-benefit ratio and analytic
decision making. They point out easy ways of applying
these basic principles to everyday diagnostic and thera­
peutic decision making. The authors obviously have had
experience in teaching these basic concepts to physicians
long unaccustomed to statistical formulation.

**Weaknesses:** Some of the cartoons could be somewhat
more professionally done.

**Recommended Audience:** This book would be useful for
medical students, house officers, and practicing physicians.

**Critical Appraisal:** Over 100 years ago, Sir William
Osler’s person-to-person bedside approach became the
model for medical training in the United States in the 20th
century. But this “eminence”-based medical model is now
vying with the “evidence”-based model, particularly as we
invent increasing numbers of tests and therapeutic options
that force an emphasis on considering cost-benefit ratios.
An understanding of the importance of medical statistics,
the application of Bayes’ theorem, and probability equa­
tions will become an imperative part of all aspects of
medical care. This book makes a substantial contribution to
this trend.
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Ophthalmic Ultrasound: A Diagnostic Atlas, 2nd Edition


Scope: This book represents an extensively updated version of the successful first edition published in 1998 and co-authored by Cathy DiBarnardo, Andrew Sehachat, and Sharon Fekrat. This new volume highlights the major advances in ophthalmic ultrasound developed and improved over the past decade and more clearly expands the echographic characteristics of a wide variety of ocular and orbital lesions.

The book is divided into 11 chapters. An introductory chapter presents a thorough review of basic screening techniques and labeling conventions. A single chapter devoted to the anterior segment has been extensively expanded with many new images, including excellent photos using the 20 and 50 MHz (UBM) probes. These include a wide variety of common and unusual disease processes. Three chapters, “Vitreous,” “Retina,” and “Choroid,” cover posterior segment disease. The previous chapter on orbital disease has been divided into three new chapters covering the retrobulbar optic nerve, extraocular muscles, and orbital lesions. There is a separate chapter on ocular trauma, and a very comprehensive chapter on intraocular tumors. A final chapter briefly discusses biometry and some unusual conditions such as glaucoma valves and scleral buckles. Each chapter has a small but useful list of selected references for those who wish to explore the subject further.

Strengths: The major strength of this book is its authors, both of whom have many years of experience in an academic ultrasound facility. The atlas includes more than 550 high-quality figures to illustrate examination techniques and ultrasonic characteristics of more than 100 disease processes. It provides a quick pictorial reference guide for common disorders encountered in clinical practice, clearly demonstrating their characteristic echographic features. The book is easy to use and conditions are grouped conveniently by anatomic region of the eye and orbit. The figures are nicely labeled with arrows or letters indicating the sites of pathology.

Weaknesses: The most important weakness of this book is the scant and largely absent correlation between clinical and histologic characteristics of disease processes and corresponding echographic findings. Such correlation would help the reader understand what is represented on the images. Also missing is any discussion of the physics of ultrasonography to give an understanding of how various components of the image are generated. In addition, there is also no discussion of various probe frequencies, when and why they are used, or how they give different types of information. Finally, it is widely acknowledged that the results of ophthalmic ultrasonography are extremely operator dependent. This book, like most similar volumes, does not discuss any details of artifacts, why they can be misinterpreted, and how they can be avoided by the operator. This information would be very useful for the novice ophthalmic user who is not a professional echographer.

Recommended Audience: This book will be a welcome addition to the library of ophthalmic care providers—those in practice and those in training, physicians, and non-physicians. It will also be useful for non-ophthalmic echographers and radiologists who occasionally examine the eye.

Critical Appraisal: Cathy DiBernardo and Ellen Greenberg, widely respected authorities on ophthalmic ultrasound, have brought their considerable expertise to this atlas. The book serves primarily as a reference comparative atlas to be used by those performing such echography. It will not serve the needs of individuals who are seeking a more comprehensive understanding of ultrasonography and its components as a diagnostic instrument.

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Clinical and Basic Oculomotor Research


Scope: This book contains a collection of papers (42 platform and 33 posters) presented at a satellite meeting of the Bárány Society. The meeting, “Clinical and Basic Ocular Motor Research,” was held in Siena, Italy, from July 3–5, 2004 and celebrated the 60th birthday of David S. Zee. The papers are well illustrated, concise, and clearly written. As the editors stated in their preface, the aim of the volume was to provide researchers with a state-of-the-art update and foster the interaction between basic and clinical researchers and the translation of their research to bedside treatment.

The book is divided into seven sections. Consistent with the primary thrust of Dr. Zee's research—to improve the diagnosis and treatment of patients with ocular motor
and vestibular disorders—the major sections of the book are entitled, “Part II. Vestibulo-Ocular Reflex,” “Part III. Saccades,” and “Part VI. Pathophysiology.” The remaining sections, “Part I. Extraocular Muscles,” “Part IV Pursuit, Vergence, and Ocular Following,” “Part V. Psychophysics,” and “Part VII. Short Papers” provide selections in other important areas of ocular motor research.

Strengths: The papers in this book reflect the expertise of their authors, all knowledgeable in ocular motor control. The breadth of topics guarantees that there is something for every one with an interest in normal and abnormal ocular motor function. One particular gem is the paper on proprioception in the extraocular eye muscles. Virtually ignored for four decades, the putative role of proprioception in the ongoing calibration of the ocular motor system has finally become the subject of anatomic and physiologic research. Another fine paper establishes the beneficial effects of yellow filters on magnocellular function, especially motion detection, suggesting that such lenses would benefit those with nystagmus, who have elevated motion-detection thresholds.

Weaknesses: I would have liked to see more on nystagmus, in all its forms. However, research need not be directed at a specific topic to have basic and clinical relevance to that topic.

Recommended Audience: This book successfully reaches its target audience—basic and clinical researchers. It would also be worthwhile reading for all physicians whose specialty includes diagnosing and treating ocular motor disorders. They may make the critical inferences that enable additional transitions from the data and conclusions found in the papers in this book to better diagnosis and treatment, the goal of Dr. Zee.

Critical Appraisal: This is one of a long series of conference-initiated books that must be on the shelves of all ocular motor researchers if they are to remain current. State-of-the-art research by experienced scientists in their fields; what more could you ask for?

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Fundamentals of Neurology: An Illustrated Guide


Scope: This is the fifth edition of an English translation of a venerated Swiss textbook of neurology aimed at medical students. As a full-size paperbound book of nearly 300 pages and 396 illustrations, it amply covers the standard subject matter in the field, including history-taking, the neurologic examination, localization of lesions, and the principal brain and spinal cord disorders. The authors write succinctly and rely heavily on tables and schematic illustrations.

Strengths: The authors have deftly summarized the important principles of neurologic diagnosis and highlighted the “pearls.” The writing is excellent. You would never know that the original version was not in English. As with Thieme publications, each page is handsomely laid out so that text and illustrations balance and enhance one another. The schematics are brilliant—elegant and simple, yet accurate and informative. The production values—fonts, paper, binding, glossy paper, quality of reproduction of MRI scans, and use of two-color format (red and black)—are of highest quality.

Weaknesses: Much of the material is déjà vu for practitioners of neurology.

Recommended Audience: Medical students and neuro-ophthalmologists, and perhaps ophthalmologists and neurosurgeons would find this book useful.

Critical Appraisal: This is a beautifully constructed work of fine pedagogy. I cannot imagine a more aesthetic, accessible presentation of clinical neurology. It works as an introduction or recapitulation of the field. Check it out.

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Ultimate Review for the Neurology Boards


Scope: This book targets those preparing for the neurology board examination, a written and oral examination. The oral examination will be phased out in 2009. The book provides a brief overview of the content of the oral examination and practical tips on preparing for it and taking it. The lion’s share of the book is directed to dispensing information appropriate for the written examination.

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As the goal is to present many facts with minimal text, the authors use outline form. The alternative source for such a review is a book by Geyer et al, which is even more telegraphic. This book provides more context for the "pearls."

The chapters are thematically organized. Standard clinical topics and clinical neurophysiology are covered in the first half of the text. The second half addresses pediatric neurology, psychiatry, brief treatments of some neurology-related subspecialties, and several basic neuroscience topics identified by the American Board of Psychiatry and Neurology as featured areas of examination.

Some chapters are minimalistic in their outline presentation, whereas others are so detail-packed that they take on a paragraph-like feel. Most are in between, with a recognizable outline format that occasionally blossoms into sentences or near sentences when the author wishes to stress an important point or provide additional context. There is a companion Web site for this book, which offers computerized "flash cards" and abbreviated clinical vignettes. The Web site material also doubles as a self-test section.

Strengths: This book touches on a huge body of information in a well-organized fashion. The Web site resource is particularly useful, especially for illustrations.

Weaknesses: As with most outline-formatted review books, the staccato presentation neither transports the reader nor provides enough context to provide true understanding of the facts presented. But this book is not meant to serve as a primary source of learning, rather it serves as a review of previously learned material. The reader will not be able to rely on this book as a thorough review. For example, neuroradiology and neuropathology are not addressed. Inaccurate or mistaken information is occasionally presented.

Recommended Audience: Board-eligible neurologists looking for a big-picture review of information encountered during their residency will appreciate this book. Others who may benefit from this book include neurologists planning to take their 10-year recertification examination. Neurology residents preparing for their in-service examination would benefit from a read-through.

Critical Appraisal: This book is a compromise between a neurology house officer’s survival guide and a detailed review outline. Those who like either type of book will want to check this one out. It can certainly help consolidate previously acquired information. Trainees with large areas of knowledge deficits will need a more comprehensive and intensive approach to prepare adequately for the board examination.

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Upcoming Meetings

31st Annual Meeting of the American Society of Neuroimaging
Tucson, AZ
http://asnweb.org
Contact: asn@llmsi.com

Feb. 20–Feb. 22, 2008
International Stroke Conference
New Orleans, LA
http://strokeconference.americanheart.org/portal/stroke/conference/sc/
Contact: strokeconference@heart.org

March 8–March 13, 2008
34th North American Neuro-Ophthalmology Society (NANOS) Annual Meeting
Orlando, FL
http://www.nanosweb.org/meetings/index.htm
Contact: info@nanosnet.org

April 2–April 6, 2008
American Association of Pediatric Ophthalmology & Strabismus (AAPOS) Annual Meeting
Washington, DC
http://www.aapos.org
Contact: aapos@aao.org

April 12–April 19, 2008
60th Annual Meeting of the American Academy of Neurology (AAN)
Chicago, IL
http://am.aan.com/
Contact: membership@aan.com

April 26–May 1, 2008
76th American Association of Neurological Surgeons (AANS) Annual Meeting
Chicago, IL
Contact: info@aans.org

April 27–May 1, 2008
Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting
Ft. Lauderdale, FL
http://www.arvo.org
Contact: arvo@arvo.org

May 13–May 16, 2008
European Stroke Conference
Nice, France
http://www.eurostroke.org/esc_congresses.htm
Contact: hennerici@eurostroke.eu

May 15–May 17, 2008
Asian Neuro-Ophthalmology Society (ASNOS) Taipei, Taiwan
Contact: asnos2008@yahoo.com.tw

May 18–May 20, 2008
Society of Neurological Surgeons Annual Meeting
Madison, WI
http://www.societyns.org/meeting/index.html

May 18–May 24, 2008
18th International Visual Field and Imaging Symposium (International Perimetric Society)
Nara City, Japan
http://www.congre.co.jp/ips2008/
Contact: ips2008@congre.co.jp

June 1–June 5, 2008
46th Annual Meeting of the American Society of Neuroradiology (ASNR)
New Orleans, LA
Contact: meetings@asnr.org

June 7–June 12, 2008
18th Meeting of the European Neurological Society
Nice, France
http://www.akm.ch/ens2008
Contact: ensinfo@akm.ch

June 7–June 12, 2008
International Neuro-Ophthalmology Society (INOS)
Napa, CA
Contact: info@inos2008.org

June 11–June 14, 2008
Canadian Ophthalmological Society Annual Meeting
Whistler, BC
http://www.eyesite.ca/english/calendar.htm
Contact: kross@eyesite.ca
June 24–June 27, 2008
**XIX Symposium of the International Society on Metabolic Eye Disease**
Guangzhou, China
Contact: optoedcorp@aol.com

June 26–June 29, 2008
**50th Annual Scientific Meeting of the American Headache Society**
Boston, MA
http://www.americanheadachesociety.org
Contact: ahsmtgs@talley.com

June 28–July 2, 2008
**World Ophthalmology Congress**
**XXXI International Congress of Ophthalmology**
**XII Chinese Ophthalmology Symposium**
**XX Hong Kong Ophthalmological Symposium**
Hong Kong
http://www.woc2008hongkong.org/
Contact: info@woc2008hongkong.org

July 9–July 11, 2008
**31st Annual Meeting of the Japanese Neuroscience Society**
Tokyo, Japan
Contact: neurosci2008@congre.co.jp

July 12–July 16, 2008
**6th Forum of European Neuroscience Societies FENS**
Geneva, Switzerland
http://fens2008.neurosciences.asso.fr/
Contact: gibson@mdc-berlin.de

Aug. 23–Aug. 26, 2008
**12th Congress of the European Federation of Neurological Societies (EFNS)**
Madrid, Spain
http://efns2008.efhs.org/
Contact: efhs08@kenes.com

Sept. 20–Sept. 25, 2008
**Congress of Neurological Surgeons 58th Annual Meeting**
Orlando, FL
http://www.neurosurgery.org/meetings/meetingsites.asp
Contact: info@cnos.org

Sept. 21–Sept. 24, 2008
**133rd Annual Meeting of the American Neurological Association**
Salt Lake City, UT
http://www.aneuroa.org
Contact: julieratzloff@llmsi.com

**XVIII International Congress of Eye Research (ICER)**
Beijing, China
http://www.chinamed.com.cn/2008icer
Contact: gejian@mail.sysu.edu.cn

Sept. 24–Sept. 27, 2008
**6th World Stroke Congress**
Vienna, Austria
http://www.kenes.com/stroke2008/
Contact: stroke2008@kenes.com

Nov. 8–Nov. 11, 2008
**Annual Meeting of the American Academy of Ophthalmology (AAO)**
Joint Meeting with the European Society of Ophthalmology (SOE)
Atlanta, GA
http://www.aaao.org/meetings/annual_meeting/future.cfm
Contact: meetings@aaao.org

Nov. 15–Nov. 19, 2008
**38th Annual Meeting of the Society for Neuroscience**
Washington, DC
http://www.sfn.org/index.cfm?pagename=annualmeeting
Contact: info@sfn.org

Feb. 21–Feb. 26, 2009
Lake Tahoe, CA
http://www.nanosweb.org/meetings/index.htm
Contact: info@nansonet.org

June 17–June 20, 2009
**European Neuro-Ophthalmology Society (EUNOS)**
Luebeck, Germany
http://www.eunos2009.org
Contact: detlef.koempf@neuro.uni-luebeck.de
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