EDITORIAL

Endovascular Treatment of Dural Carotid Cavernous Sinus Fistulas

Ajay K. Wakhloo

ORIGINAL CONTRIBUTIONS

Successful Treatment of Six Cases of Indirect Carotid-Cavernous Fistula with Ethylene Vinyl Alcohol Copolymer (Onyx) Transvenous Embolization

Karthik D. Bhatia, Lily Wang, Richard J. Parkinson, and Jason D. Wenderoth

Successful Transarterial Embolization of a Barrow Type D Dural Carotid-Cavernous Fistula with Ethylene Vinyl Alcohol Copolymer (Onyx)

Deeraj Gandhi, Sameer A. Ansari, and Wayne T. Cornelis

Restricted Diffusion in the Optic Nerve and Retina Demonstrated by MRI in Rhino-Orbital Mucormycosis

Hattie Gu Hapitpong, Muge Onbasigo Gulbul, and Enis Yüksel

Restricted Diffusion in the Superior Ophthalmic Vein and Cavernous Sinus in a Case of Cavernous Sinus Thrombosis

Hemant Parmar, Deeraj Gandhi, Suresh K. Mukherji, and Jonathan D. Trobe

Direct Carotid-Cavernous Fistula Causing Brainstem Venous Congestion

Miguel Bussière, Stephen P. Lownie, David M. Fels, and David Nicolle

Gaze-Evoked and Rebound Nystagmus in a Case of Migrainous Vertigo

Sun-Young Oh, Min-Wook Seo, Young-Hyun Kim, Kwang-Dong Choi, Dae-Seong Kim, and Byoung-Soo Shin

Temporary Adduction Deficit After Nasal Septoplasty and Radiofrequency Ablation of the Inferior Turbinate

Saed Aftghehli, S. Hossein Alimohammadi, Mohammad Hossein Baradaranfar, and S. Abbas Mirvakili

Pupil Perimetry Demonstrates Hemifield Papillary Hypokinesia in a Patient With a Paretic Lesion Causing a Relative Afferent Pupil Defect but No Visual Field Loss

Eleni Papageorgiou, Thomas Wermund, and Helmut Wilhelm

Perceptual Distortion in Homonymous Paracentral Scotomas

Nikolaos A. Mavrokantas, Nathalie P. L. Dong-Burgner, Erika N. Larinica, Theodor Landis, and Avinash B. Sofian

(continued on next page)
LETTERS TO THE EDITOR

Opioclonus Caused by Diphenhydramine Self-Poisoning
Takashi Irioka, Ayako Yamamura, Naoki Uchida, Mariko Iwase, Hajime Yanuhara, and Hidehiro Mizusawa

See-Saw Nystagmus in a Patient with Wallenberg Syndrome
Jesus Porta-Etessean, Ignacio Casanova, Beatriz Pazuelo, Daniella Di Cupua, Javier del Val, Maria Eugenia Garcia Garcia, and Alberto Marcos

Another Case of Paroxysmal Tonic Downgaze in Infancy
Meropi Tsoufi, Polyxeni Stelimitri, Alexandros Makis, and Antigone Stournopoulou-Mavridou

Leber Hereditary Optic Neuropathy Associated with Malabsorption Syndrome After Bariatric Surgery
Diego Santos-Garcia, Javier Abella, Begoña De Domingo, and Rafael de la Fuente-Fernández

Perinatal Head Tilt in Congenital Superior Oblique Palsy
Michael C. Brodsky and Virginia Karlsson

BOOK REVIEWS

Andrew G. Lee
78 Rapid Diagnosis in Ophthalmology: Neuro-Ophthalmology
   John B. Selhorst
79 Neuro-Ophthalmology [Blue Book of Neurology Series]
   Nicholas J. Volpe
   Kathleen B. Digre
80 The Pseudotumor Cerebi Syndrome: Pseudotumor Cerebi, Idiopathic Intracranial Hypertension, Benign Intracranial Hypertension, and Related Conditions
   Michael Wall
81 Rapid Diagnosis in Ophthalmology: Pediatric Ophthalmology and Strabismus
   R. Michael Siatkowski
81 Oxford Handbook of Ophthalmology
   Laura D. Cook
82 Garner and Klintworth’s Pathobiology of Ocular Diseases, 3rd Edition
   Ben Glasgow
   Paul T. Diamond
83 Visual Perception Part 2: Fundamentals of Awareness, Multi-Sensory Integration and Higher-Order Perception
   Ipek Oruc and Jason J. S. Barton
83 Neuromatology Through Clinical Cases
   Edward Margolin
84 Case Studies in Stroke: Common and Uncommon Presentations
   Andrew M. Soutterland and Bradford B. Worrall
85 17th International Neuro-Ophthalmology Society (INOS) Meeting Napa, California, June 7-12, 2008
   Neil R. Miller
   Kathleen B. Digre

CALENDAR
Endovascular Treatment of Dural Carotid Cavernous Sinus Fistulas

Ajay K. Wakhloo, MD, PhD

With the introduction of newer embolization materials and flat panel detectors to the surgical angiography unit and refinement of endovascular techniques, we are witnessing rapid improvement in the safety and efficacy of treatment of direct and dural carotid-cavernous sinus fistulas (CCFs). In this issue of the Journal of Neuro-Ophthalmology, Gemmete et al (1) provide an overview on the clinical presentations, Barrow classification, and typical CT and MRI findings of CCFs. The authors then focus on the history of endovascular CCF treatment and introduce us to transarterial, transvenous, and combined transarterial-transvenous approaches. They point out that treatment options range from manual compression of the carotid artery, radiation therapy, stent and stent grafts (predominantly for direct CCFs), placement of detachable balloons or coils within the arteriovenous connection, and infusion of embolic materials into the CCF. Depending on the experience and preference of the treating physician, embolic materials are frequently combined.

The articles by Gandhi et al (2) and Bhatia et al (3) describe the use of Onyx for dural CCF. Recently approved by the Food and Drug Administration (FDA) for preoperative embolization of brain arteriovenous malformations (bAVMs), Onyx is an ethylene vinyl alcohol copolymer in a dimethyl sulfoxide solvent. This liquid embolic mixture also contains suspended tantalum powder that gives it radioopacity and its trademark black color. Onyx is a nonadhesive polymer that precipitates in the vessel as the solvent is diluted and washed out. The authors emphasize the safety profile of Onyx resulting from the nonadhesive nature of the material, which permits a long and controlled infusion and a significant reduction in procedure time and radiation exposure.

Although a controlled and long injection is desirable, it entails the risk of occluding pial arteries through dural anastomoses. Unlike cyanoacrylates, which are mixed with iodinated oil and well visible (4), Onyx may be poorly visualized in smaller vessels owing to sedimentation of tantalum powder within the delivery microcatheter. This feature demands advanced knowledge of “dangerous” preexisting extracranial-intracranial anastomoses frequently not visible before embolization. Gandhi et al (2) and Bhatia et al (3) emphasize the danger of Onyx infusion into preexisting collateral vessels. To avoid reflux of the embolic agent, use of a nondetachable temporary balloon within the internal carotid artery is recommended if the pretreatment angiogram shows that the fistula is substantially supplied by the meningohypophyseal trunk.

Although 6 patients treated successfully is a small number, the authors provide evidence that Onyx is a promising new embolic agent for treatment of dural CCFs. Several studies have now been published on the successful use of Onyx alone or in conjunction with coils and stents for direct and dural CCFs and other dural arteriovenous fistulas (AVFs) (5–10). Although cure of dural CCFs and other AVFs is reported in most treated patients with no major periprocedure morbidity, large series demonstrate that the treatment of AVMs remains challenging (5–11). Although use of Onyx was initially promising, larger case series show that cure of bAVMs with Onyx is achieved in only 2%–28% of patients, and
there is permanent morbidity and mortality of 3% to 11%. In experienced hands, an increased cure rate may be attainable, but the complication rate remains comparable to that of formerly used liquid embolic agents (11,12).

As Bhatia et al (3) discuss, endovascular treatment of dural CCFs can be lengthy and may involve significant radiation exposure owing to the time needed to place the microcatheter in hard-to-access dural CCFs rather than to the time needed to deploy embolic materials. As the numbers of x-ray-based endovascular procedures increase, there is a growing concern about long fluoroscopy exposure (13,14). The goal remains to avoid skin injuries and damage to the lens from increased radiation exposure. In a recent study, the surface doses recorded during endovascular procedures were equivalent to a dose of 1.5 Gy, which may increase the risk of inducing meningiomas, gliomas, and nerve sheath tumors (15).

Experience over the past 3 decades has shown that endovascular treatment of CCFs is safe and should be considered the primary option. However, as with any new technology, caution is warranted with the latest embolic material until more patients have been treated. Long-term clinical and angiographic data on Onyx are needed to verify the permanency of CCF occlusion. As with cyanoacrylates, Onyx seems to generate a chronic inflammatory response, which may be important for lasting obliteration of any type of arteriovenous fistula (16,17).

REFERENCES
Successful Treatment of Six Cases of Indirect Carotid-Cavernous Fistula with Ethylene Vinyl Alcohol Copolymer (Onyx) Transvenous Embolization

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Background: Endovascular transvenous treatments have become the mainstay in the management of indirect carotid-cavernous fistulas (CCFs). However, the standard coil techniques are associated with a substantial failure and complication rate. The ethylene vinyl alcohol copolymer (Onyx) Liquid Embolization System has advantages over coils, including the ability to penetrate and occlude vessels of small caliber or with difficult access.

Methods: This was a review of 5 consecutive patients with indirect type D CCFs who underwent 6 procedures using the Onyx system alone at the Prince of Wales Hospital, Sydney, between December 2005 and May 2007. The cavernous sinus was catheterized with MTI Echelon-10 or Rebar-14 microcatheters via the femoral vein using an inferior petrosal approach to the cavernous sinus in 5 procedures and directly via the superior ophthalmic vein in 1 procedure.

Results: All 5 patients had complete closure of the fistulas as seen on imaging and full reversal of ophthalmic manifestations without lingering complications and with substantially shorter procedure times than with conventional approaches.

Conclusions: The Onyx system is a safe and useful method of closing indirect CCFs transvenously. This is the first series report of the use of the Onyx system alone in the treatment of these vascular abnormalities.

Carotid-cavernous fistulas (CCFs) are uncommon but clinically significant vascular anomalies that may be associated with serious neurologic or ophthalmic morbidity. The most commonly used classification system of CCFs is that proposed in 1985 by Barrow et al (1), consisting of four different grades (A–D) based on angiographic identification of the arterial feeding sources of the fistula (1,2). All 6 cases of the indirect CCFs in this series were Barrow type D fistulas, defined as having arterial feeding sources from both the internal carotid artery (ICA) and external carotid artery (ECA) (1–3).

Endovascular treatments have become the mainstay in the management of indirect CCFs over the last 20 years (2–7). The occlusion of the complex vessel network via endovascular approaches using standard balloon and coil techniques has been difficult, however, because the honeycomb morphology of the cavernous sinus is not amenable to these large and stiff devices, and the result sometimes is incomplete closure of the fistula with resultant worsening in morbidity associated with shunting into orbital or cortical venous systems (2,4,6,8–10). In addition, coil and balloon techniques are associated with a high rate of mechanical cranial nerve injury (4,5).

Liquid embolic systems such as pure ethanol and n-butyl cyanoacrylate (nBCA) are increasingly being used as adjuncts or alternatives to balloon and coil systems owing to the liquid's ability to penetrate and occlude vessels of small caliber or with difficult access (11–13). However, the liquid poses a small but significant risk of venous and arterial thromboembolism via spontaneous droplet movement (11,13).

The ethylene vinyl alcohol copolymer (EVOH, Onyx) liquid embolization system (MicroTherapeutics Incorporated, Irvine, CA) uses a polymer that precipitates into an artificial embolus upon contact with blood or bodily fluids (12,14,15). This system possesses all of the advantages of other liquid embolic systems but allows greater control of polymer distribution, thus potentially reducing the risk of spontaneous droplet movement. It can fill cavities in a manner similar to that of foam-based embolization products (12,14,15). Unlike nBCA, Onyx also precipitates in a coherent fashion rather than having a tendency to
fragment. It can be delivered over much more prolonged periods because of its nonadhesive nature (14,15,16). The relative simplicity of CCF occlusion with Onyx compared with standard coil occlusion techniques has the potential to reduce angiographic screening times and thereby patient radiation dose.

We present 6 type D CCFs in 5 patients treated only with the Onyx system via a transvenous approach.

METHODS

Five consecutive patients with indirect type D CCFs were treated from December 2005 until May 2007 at the Prince of Wales Hospital, Sydney, Australia, using the Onyx system via a transvenous approach. Three of the patients were women, aged 44, 54, and 64 years at the time of treatment, and two were men, aged 63 and 64 years at the time of treatment. All endovascular procedures were undertaken by experienced neurovascular interventionalists (JW and RP).

Onyx was chosen as the sole embolization agent for these patients because of its theoretical advantages in reducing screening times, its ease and flexibility of use, and the theoretical reduction in risk of incomplete closure, cranial nerve injury, adhesive complications, and thromboembolism. In none of the 6 patients was there a need to use alternative embolic products.

The Onyx system consists of a copolymer that is dissolved in a dimethyl sulfoxide (DMSO) solvent (15). Within this mixture there is a suspended micronized tantalum powder that allows fluoroscopic visualization. When this liquid mixture is delivered via a catheter to the desired site, it makes contact with blood that causes the DMSO solvent to diffuse away rapidly, resulting in precipitation of the EVOH polymer into a putty-like mass with radiopaque properties (12,15). The nature of the precipitation process is such that the layer of Onyx in contact with blood forms a skin, the center of the precipitating mass remaining in its dissolved state (15). As pressure is applied to the delivery syringe, the liquid Onyx ruptures the overlying skin at its weakest points much as lava flows occur on the ocean floor. The specific formulation used in this series was Onyx-34, which has a nominal liquid viscosity of 34 centistokes (15). This formulation has relatively high viscosity so as to reduce the risk of retrograde penetration into the ICA.

In our patients, the liquid was delivered by an MTI Rebar-10 microcatheter in Case 1 and by an MTI Echelon-10 microcatheter in all other cases in accordance with the manufacturer's instructions (15).

All 5 patients had pretreatment imaging of the fistulas via time-resolved magnetic resonance angiography (TR-MRA) and digital subtraction angiography (DSA). All catheterization was completed under full anticoagulation using heparin to achieve an activated clotting time of 250–300 seconds. All procedures were performed under general anesthesia. DSA was used to obtain views of right and left internal carotid, external carotid, and vertebral arteries before treatment via catheterization of the femoral artery.

A catheter was maintained in the arterial system at all times to allow visualization of the arterial side of the fistula. The diagnostic angiograms were closely studied for supply of the fistulas by inferolateral or meningohypophyseal branches of the ICA. Such supply would be a relative contraindication to the use of Onyx or would necessitate the use of balloon protection in the ICA during Onyx injection.

The cavernous sinus was catheterized via the femoral vein using an inferior petrosal approach in 5 procedures. In 1 patient, in whom there were bilateral CCFs, a second treatment was required, necessitating access to the opposite cavernous sinus via the superior ophthalmic vein, which was cannulated under transorbital ultrasound guidance.

The initial targeted point of embolization in all cases was the venous point that filled first on contrast injection from the arterial side of the fistula, but this was not always necessary. Onyx-34 was progressively delivered into the cavernous sinus until complete obliteration of the sinus and the fistula was achieved.

The average angiographic screening time for the 5 procedures was 36.58 minutes. In 1 procedure, the screening time could not be obtained because of equipment failure. Confirmatory post-Onyx DSA films were obtained from the arterial supply to demonstrate definitive closure of the fistula. All patients were examined after the procedure to assess the efficacy of the treatment by imaging and clinical criteria. Follow-up included MRI and ophthalmologic evaluation at 3 months after treatment.

RESULTS

Table 1 shows clinical and imaging features of our 5 patients.

Case 1

A 63-year-old man had a 2-week history of redness of the right eye. Four days before presentation, he had noted double vision on looking to the right and then began to have a progressive reduction in the vision of his right eye. He was found to have ptosis, exophthalmos, and chemosis of the right eye. There was a significant reduction in visual acuity in the right eye. Dipsopia was present on right, upward, and downward gaze, and there was an obvious abduction deficit of the right eye. There were no other pertinent clinical abnormalities.

TR-MRA showed a right-sided Barrow type D CCF fed by right ICA and ECA branches (Fig. 1A–B). Given the rapid progression in symptoms and the risk of blindness to
the right eye, he underwent endovascular management of the lesion with the Onyx system the next day. Transvenous embolization was achieved using the Onyx-34 Liquid Embolization System with an MTI Rebar-10 catheter via an inferior petrosal approach from the right femoral vein. The cavernous sinus was progressively and completely obliterated with Onyx. Post-Onyx DSA views demonstrated definitive closure of the fistula (Fig. 1C). Total screening time was 37.6 minutes. There was an immediate dramatic reversal in the proptosis and chemosis of the right eye. Postoperatively the patient was noted to have a right sixth cranial nerve palsy, unchanged when compared with his preprocedural status. However, on follow-up examination at 3 months, the palsy had completely resolved. Successful closure of the fistula was confirmed on follow-up MRI examination.

**TABLE 1. Clinical and imaging features of our 5 patients**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Clinical Presentation</th>
<th>Fistula Side</th>
<th>Venous Approach</th>
<th>Procedure Time (min)</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63</td>
<td>M</td>
<td>Diplopia, right eye visual loss</td>
<td>Right</td>
<td>IPS</td>
<td>37.6</td>
<td>Temporary sixth cranial nerve palsy</td>
</tr>
<tr>
<td>2</td>
<td>54</td>
<td>F</td>
<td>Diplopia, pulsatile tinnitus, left eye visual loss</td>
<td>Left</td>
<td>IPS</td>
<td>N/A</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>44</td>
<td>F</td>
<td>Headache, pulsatile tinnitus, diplopia, left eye visual loss</td>
<td>Right</td>
<td>SOV</td>
<td>23.7</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>64</td>
<td>F</td>
<td>Diplopia</td>
<td>Right</td>
<td>IPS</td>
<td>39.1</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>64</td>
<td>M</td>
<td>Diplopia, right eye conjunctival corkscrew vessels</td>
<td>Right</td>
<td>IPS</td>
<td>22.5</td>
<td>None</td>
</tr>
</tbody>
</table>

IPS, inferior petrosal sinus; SOV, superior ophthalmic vein; N/A, not available.

**Case 2**

A 54-year-old woman presented with a 3-week history of blurred vision and painful movements of the left eye. For 10 days before presentation, she had had double vision upon looking to the left and a persistent whooshing sound in both ears. She was found on examination to have reduced visual acuity, conjunctival congestion, and mild proptosis of the left eye. There was also reduced abduction of the left eye. Noncontrast CT imaging revealed dilated superior ophthalmic veins bilaterally.

DSA demonstrated a complex left type D CCF with arterial supply bilaterally from the ICA and ECA (Fig. 2A–B). There was also a right type D CCF. The left cavernous sinus was accessed via an inferior petrosal approach from the right femoral vein and was successfully embolized using the Onyx-34 Liquid Embolization System with an

**FIG. 1.** Digital subtraction angiography of Case 1. Midarterial (A) and late arterial (B) phase lateral right internal carotid arteriograms show fistulous opacification of the right cavernous sinus (arrow) and superior ophthalmic vein (arrowhead). Lateral right internal carotid arteriogram (C) after the deployment of Onyx into the cavernous sinus via a transvenous approach shows total occlusion of the fistula.
MTI Echelon-10 microcatheter. Post-Onyx views revealed closure of the complex left CCF (Fig. 2C). Screening time of this procedure could not be obtained because of imaging equipment failure at the end of the procedure. The patient had made a full clinical recovery by the time of discharge. The right fistula (Fig. 2D) was closed 3 months later using the same Onyx-34 technology. Because of the known occlusion of the inferior petrosal sinus, the right cavernous sinus was accessed via the right superior ophthalmic vein (SOV) using transorbital ultrasound guidance for catheterization of this vessel (Fig. 2E). The right cavernous sinus was closed using Onyx-34. Post-Onyx DSA views confirmed closure of the fistula. Screening time was 23.7 minutes. There was some moderate postoperative conjunctival edema of the right eye, which was probably a result of the saline flushing of the right SOV. This resolved within 36 hours. The patient made a full recovery before discharge. Successful closure was confirmed on follow-up ophthalmic and MRI examination 3 months later.

Case 3
A 44-year-old woman presented with a 2-month history of severe headaches associated with nausea and vomiting in the morning. Pulsatile tinnitus, blurred vision of the left eye, and double vision on left gaze developed soon afterward. There was proptosis and conjunctival injection of the left eye, with diplopia on abduction. TR-MRA and DSA demonstrated a left CCF. The left cavernous sinus was accessed by advancing the Echelon-10 microcatheter through the right inferior petrosal sinus (IPS) and right cavernous and circular sinuses, and the fistula was successfully occluded using Onyx-34 (Fig. 3). Post-Onyx DSA views confirmed closure of the fistula. Screening time was 60.0 minutes. Ophthalmic and MRI review at 3 months after the procedure confirmed complete imaging closure and clinical recovery.

Case 4
A 64-year-old woman presented with a 6-month history of double vision on looking to the right. The right eye had also developed progressive reddening over the previous 4 months. There was conjunctival injection of the right eye without associated proptosis and diplopia on right gaze. MRA demonstrated a right type D CCF. It was successfully closed using Onyx-34 via the right IPS with an Echelon-10 microcatheter. Screening time was 39.1 minutes. The patient demonstrated complete reversal of symptoms and was discharged home the next day. The success of the treatment was confirmed on MRI and ophthalmic assessment 3 months later.

Case 5
A 64-year-old man presented with double vision on looking to the right. Arterialized conjunctival vessels were

FIG. 2. Digital subtraction angiography of Case 2. Lateral (A) and anteroposterior (B) late phase arteriograms show a complex left indirect carotid-cavernous fistula (CCF) (arrow) fed from the left internal and external carotid arteries via petrosal and left inferior maxillary arterial branches. C. After Onyx occlusion of the left CCF (arrow), a right CCF is exposed (arrowhead). D. Arteriogram shows filling of the right CCF via branches of the right external carotid artery. E. The right cavernous sinus is accessed via a catheter in the superior ophthalmic vein. F. Lateral arteriogram shows complete closure of the right CCF by Onyx cast (arrow).
present in the right eye. DSA confirmed the TR-MRA evidence of a right type D CCF. The fistula was successfully closed after embolization of the right cavernous sinus with Onyx-34 delivered via a right IPS approach with an Echelon-10 microcatheter. Screening time was 22.5 minutes. There was complete reversal in the patient's symptoms postoperatively. Follow-up at 3 months with MRI and ophthalmic examination confirmed complete closure of the fistula and no return of ophthalmic symptoms.

The only possible complication among these patients was a temporary sixth nerve palsy in Case 1, which had resolved completely at the time of follow-up 3 months later.

**DISCUSSION**

We have reported successful closure without enduring complications of six Barrow type D CCFs in 5 patients using the Onyx Liquid Embolization System via a transvenous approach.

The major advantage of liquid systems such as the one we used is their ability to conform to irregular and complex vascular structures (11,13,14). However, these agents have historically been difficult to control owing to their liquid nature, which can render them dangerous because of the risks of occlusion of important vascular structures (11,13). The use of pure ethanol as a liquid embolization agent for endovascular procedures was first described by Yakes et al (17) in a series of 17 patients with cerebral vascular malformations. That series demonstrated the efficacy of the agent to cause vessel sclerosis but at the cost of a high complication rate, with 8 of 17 patients having significant neurologic deficits (11,17). Such high complication rates are in part a result of ethanol's immediacy and reliability as a sclerosing agent, such that unwanted distribution of the agent resulted in cerebral infarction (11,17).

The next developmental stage involved the use of nBCA. This agent allows greater user-based control and thus has a reduced risk of cerebral infarction (12,13,18). Wakhloo et al (13) demonstrated this advantage in a series of 14 indirect CCFs in which angiographic and clinical cure was achieved with nBCA alone (n = 6) or in combination with coil embolization (n = 7) or polyvinyl alcohol (n = 1). Only one patient had spillage of an nBCA droplet into a cerebral vessel, a substantial improvement on the results of ethanol-based procedures (13). However, perforation of the inferior petrosal sinus during microcatheter placement was encountered in one patient as the result of catheter adhesion (12,13). The adhesion of microcatheters to the vessel wall with nBCA was also described by Debrun et al (19), who encountered 29 episodes of catheter adhesion in a series involving brain arteriovenous malformation embolizations.

The Onyx Liquid Embolization System has the ability to penetrate the complex network of vessels typical of indirect type D CCFs. In addition, it also has several properties that render it superior to other liquid-based systems such as pure ethanol and nBCA. Onyx is non-adhesive, maintains excellent penetrative ability for complex vascular structures, allows greater user-based control to reduce the risk of accidental embolization, and can be delivered via a single slow injection (11,12,13,16,20,21).

The use of Onyx to treat indirect CCFs was first described in a single indirect CCF by Arat et al (16) in 2002. This same team later demonstrated its successful use...
in treatment of a superior sagittal sinus dural arteriovenous fistula (dAVF) (14). Suzuki et al (12) demonstrated the safe and effective use of Onyx in combination with detachable coils for the treatment of 3 indirect CCFs. Baccin et al (20) also described the use of Onyx in association with coils for the treatment of a single direct CCF. Before this report, no series of patients had been published in which the Onyx system was used as a single treatment technique for indirect CCFs, despite increasing theoretical and clinical evidence demonstrating its advantages over other liquid embolic systems.

The major drawback associated with the use of Onyx is the risk of retrograde penetration into the feeding arterial vessels of the fistula. This risk is particularly important in indirect CCFs when there is significant supply of the fistula by meningeal branches of the ICA, such as the inferolateral or meningohipophyseal trunks. Retrograde arterial penetration has been reported previously by Nogueira et al (22) in 12 intracranial dAVFs treated with Onyx as a single treatment technique. They noted that such retrograde penetration into arterial feeding systems had the potential to result in cerebral infarction, although this did not occur. Van Rooij et al (23) reported major cerebral infarctions as a result of such retrograde penetration in 2 of 44 patients with brain arteriovenous malformations (AVMs). Difficulty in visualizing the tiny arterial feeding vessels as they enter the cavernous sinus in indirect CCFs may allow accidental penetration of Onyx into the ICA, with the potential for cerebral artery embolization (22,23). The risk of this complication can be reduced by pausing the delivery of Onyx for several minutes when such reflux is visualized on fluoroscopy. The use of biplane fluoroscopy during Onyx injection will aid such visualization (22,23). In this series, we used Onyx-34 exclusively because of its higher viscosity to reduce the risk of such retrograde penetration. In addition, the diagnostic angiograms were closely studied beforehand for significant supply to the fistulas by inferolateral or meningohypophyseal trunks.

In this series we also described the use of a superior ophthalmic vein approach to the fistula (Case 2). This approach (2,8,21) is often necessary because there is a significant incidence of inferior petrosal sinus thrombosis, which interferes with access by that route.

This case series is limited by its low patient numbers, retrospective approach, and lack of a comparative cohort. As such, it is not possible to comment definitively on the overall safety and efficacy of the Onyx system in treatment of indirect CCFs via the transvenous approach. However, the excellent outcomes for patients in this series, increased control of agent delivery, reduced screening times, and lack of adhesive complications all indicate that there is great potential for the use of Onyx in the management of this condition.

REFERENCES

Successful Transarterial Embolization of a Barrow Type D Dural Carotid-Cavernous Fistula with Ethylene Vinyl Alcohol Copolymer (Onyx)

Dheeraj Gandhi, MD, Sameer A. Ansari, MD, PhD, and Wayne T. Cornblath, MD

Abstract: Endovascular occlusion via the transvenous route is the favored treatment method for dural carotid-cavernous fistulas (CCFs). Ethylene vinyl alcohol copolymer (Onyx), recently approved for treatment of arteriovenous malformations, has advantages over conventional liquid embolic agents in its nonadhesive nature, which allows for longer injections with decreased risk of catheter retention. We report the use of Onyx in the successful transarterial embolization of a dural CCF fed by arterial branches of the internal and external carotid arteries (Barrow type D) after multiple failed attempts to access the cavernous sinus transvenously. Transarterial Onyx embolization could be a valuable option in transarterial treatment of CCFs when venous access is difficult.


Dural-based carotid-cavernous fistulas (CCFs) are believed to result from dural sinus thrombosis (1). Also called indirect CCFs, they are distinct from direct CCFs (Barrow type A) that result from trauma or aneurysm rupture within the cavernous sinus (2). Dural CCFs are classified as type B, C, and D, depending on whether arterial feeders arise exclusively from the internal carotid artery (ICA) (type B), from the external carotid artery (ECA) (type C), or from both the ICA and ECA (type D) (3).

Endovascular occlusion, usually via a transvenous approach to the cavernous sinus, is the standard of care for symptomatic dural fistulas. A variety of embolic agents have been used, including detachable platinum coils, high-grade alcohol, and n-butyl cyanoacrylate (nBCA) (4). Recently, ethylene vinyl alcohol copolymer (Onyx; ev3 Neurovascular, Irvine, CA) has been successfully used in combination with detachable coils via the transvenous approach (4,5) and after covered stent placement in treatment of a recurrent dural CCF via the transarterial approach (6). We describe a case of a complex type D dural CCF that was successfully treated with transarterial embolization with Onyx after multiple failed attempts to catheterize the cavernous sinus.

CASE REPORT

A 70-year-old woman presented with sudden pain in the right eye, together with redness and proptosis of that eye. She had undergone a liver transplant and suffered chronic renal insufficiency, brittle diabetes mellitus, congestive heart failure, and severe iodine allergy.

Ophthalmologic assessment revealed best-corrected visual acuities of 20/70 in the right eye and 20/25 in the left eye. There was no afferent pupillary defect. Extraocular movements were full. Slit lamp examination showed modest chemosis and dilated, tortuous conjunctival vessels. Appplanation intraocular pressures were 20 mmHg in the right eye and 15 mmHg in the left eye. Ophthalmoscopy disclosed retinal vein tortuosity and dot-blot hemorrhages in the right eye and no abnormalities in the left eye.

Given her complicated medical history, an angiographic evaluation was considered risky and a trial of observation and close follow-up was recommended. However, she experienced worsening visual acuity and orbital soft tissue swelling.

After receiving sodium bicarbonate infusion and oral n-acetylcysteine for prevention of contrast agent–induced nephropathy, she underwent a cerebral angiogram that demonstrated a Barrow type D CCF with multiple tiny arterial feeders from the ICA and ECA bilaterally (Figs. 1 and 2). Multiple dural arterial branches opacified a septated...
right cavernous sinus (Fig. 3). The ipsilateral inferior petrosal sinus (IPS) was occluded, and there was no filling of the left cavernous sinus. Venous drainage was via an enlarged right superior ophthalmic vein (SOV), which demonstrated two areas of stenosis, one involving the junction of the cavernous sinus and SOV and the other involving the junction of the SOV and the angular vein (Fig. 3).

Under general anesthesia, a standard transfemoral 5-F diagnostic catheter was placed in the right ECA for arterial contrast agent injections. A 6-F guide catheter was navigated via transfemoral venous access over a 0.035-inch glide wire into the origin of the ipsilateral jugular vein. Using an Echelon 10 (ev3 Neurovascular) microcatheter and Synchro 14 microwire (Boston Scientific), access could be obtained into the IPS, but it did not opacify the right cavernous sinus. We were equally unsuccessful in gaining access to the right cavernous sinus via the contralateral IPS. We then punctured the right facial vein, but could not advance the microcatheter beyond the junction of the angular and superior ophthalmic veins.

Next we exchanged the right ECA diagnostic catheter for a 5-F guide catheter (Envoy, Cordis, Miami) and superselectively catheterized the distal internal maxillary artery with an Echelon 10 microcatheter. The microcatheter was flushed with normal saline, and the catheter dead space was filled with dimethyl sulfoxide (DMSO). Onyx-18 was slowly injected into the microcatheter dead space over 1 minute. Using constant fluoroscopy and intermittent control angiography, the small branches of the terminal internal maxillary artery supplying the fistula were embolized. The Onyx cast finally penetrated and filled the septated portion of the cavernous sinus that harbored the fistula (Fig. 4). A total of 1.4 mL of Onyx-18 was injected over approximately 20 minutes. The microcatheter could be withdrawn easily after termination of Onyx injection. Postprocedure angiograms confirmed complete occlusion of the fistula (Fig. 5).
There were no immediate complications. The patient had a significantly improved appearance of her right eye on the day after the procedure. Visual acuity and ophthalmic congestive features improved over the next few days. At a 3-week follow-up visit, a left abduction defect was noted, consistent with a partial sixth cranial nerve palsy. At the 12-week follow-up visit, the abduction deficit had mostly resolved, and visual acuity was back to baseline. The orbital soft tissue edema had completely resolved.

**DISCUSSION**

We have demonstrated successful occlusion of a complex Barrow type D CCF with Onyx embolization via the transarterial route. A nonadhesive liquid embolic agent, Onyx received Food and Drug Administration (FDA) approval for embolization of intracranial arteriovenous malformations (AVMs) in July 2005, but it has recently also been used in the treatment of dural arteriovenous fistulas (7–9). One of its major advantages over nBCA is its nonadhesive nature, allowing for longer injections with decreased risk of catheter retention (8). Therefore, even fairly extensive and complex fistulas can be treated in one or two sessions (8,9). In our early experience (unpublished material), catheterization of a single large pedicle can allow Onyx penetration into the fistula and the draining vein, as well as retrogradely into the branches of other arterial feeders. This feature decreases the frequent need for superselective catheterization and embolization of different arterial feeders with the use of nBCA. Nogueira et al (9) found Onyx to be more predictable and controllable than cyanoacrylates.

Dural (indirect) CCFs are often supplied by tiny meningeal branches of the ICA and ECA that are difficult to catheterize superselectively. Therefore, transvenous occlusion of the cavernous sinus has been advocated as the mainstay of endovascular treatment because of its safety and high rate of permanent success (2,10,11). The goal of treatment is obliteration of the sinus and disconnection of the arteriovenous (AV) shunt, which can be accomplished with a variety of embolic agents.

Detachable platinum coils are the most commonly used agents, but sometimes these fail to completely occlude the sinus (12). Coil placement can also be limited by the complex architecture, septation, or small size of the affected cavernous sinus. This limitation has prompted several investigators to use nBCA as an embolic agent via the transvenous approach to the cavernous sinus (2,11). In our patient, however, it was impossible to navigate the microcatheter into the diseased cavernous sinus because of an occluded ipsilateral IPS, circular sinus, and high-grade stenosis at the junction of the SOV and angular vein. Although surgical exposure of the SOV was an option, this would have entailed significant prolongation of the procedure.

We were encouraged to use Onyx via the transarterial approach on the basis of our recent success with this agent in treating dural AV fistulas (unpublished data). A unique feature of Onyx is its ability to penetrate and travel along tiny arterial branches, ultimately allowing casting of rather remote venous pouches and occluding the fistula. This property is very helpful when the vascular tortuosity or small size of feeders prevents distal navigation of the microcatheter.
Arat et al (4) first described intracavernous injection of Onyx, in combination with coils, via an IPS approach. Subsequently, Suzuki et al (5) described the combined use of coils and Onyx in 3 patients. Lv et al (6) recently demonstrated transarterial Onyx treatment of a recurrent CCF that developed a dural supply; no complications were reported.

In our patient, a temporary contralateral abduction defect was noted at the 3-week follow-up. The cause of this complication is unclear, especially as there was no penetration of Onyx into the left cavernous sinus, but it could have been an inflammatory response generated by Onyx. Delayed cranial nerve palsy has been reported with the use of nBCA (2) and coils (13). Given that the existing clinical experience of treating CCFs with liquid embolic agents is relatively limited, continued caution and close follow-up are necessary.

One limitation of our report is the lack of angiographic follow-up. The complex medical history of our patient was a caution to follow-up angiography. However, previous animal studies have shown that the results obtained with Onyx are durable. No histologic evidence of recanalization was noted in a rete swine AVM model 6 months after Onyx embolization (14). Cognard et al (8) reported that among 23 of the 24 patients with dural fistulas treated with Onyx who underwent follow-up angiography at 3 months, none demonstrated recurrent fistulas.

A note of caution is necessary with the use of Onyx in the treatment of dural fistulas. Onyx has a propensity to retrogradely fill other arterial feeders to the fistula (9,15) either via their common connection to the vein or via preexisting collateral anastomoses. Therefore, thorough understanding of the morphology of the potential arterial feeders and the fistula is necessary before Onyx embolization is undertaken. The possibility of dangerous ICA-ECA anastomoses must always be kept in mind.

REFERENCES

Restricted Diffusion in the Optic Nerve and Retina Demonstrated by MRI in Rhino-Orbital Mucormycosis

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Abstract: A 29-year-old man developed vision loss in the right eye due to orbital arteritis, cavernous sinus, and superior ophthalmic vein occlusion in mucormycosis. Diffusion MRI obtained within 2 days of symptom onset showed that the apparent diffusion coefficient values of the optic nerve and retina were remarkably decreased on the affected compared with the unaffected side. A follow-up MRI study 21 days after symptom onset revealed the anticipated disappearance of these signal changes, confirming that they were a true reflection of ischemia in the optic nerve and retina. This report adds to an accumulating body of literature on restricted diffusion in these tissues in conditions producing severe ischemia.


Diffusion imaging has been used to diagnose acute brain ischemia. Because early diagnosis is important to salvage the penumbral zone (1), this new sequence has been widely applied. Its use in spinal cord and optic nerve ischemia has only recently been reported (2–6). In this report, we demonstrate restricted diffusion not only in the optic nerve but also in the retina.

CASE REPORT

A 29-year-old man presented with complete vision loss in the preceding 3 hours. He also noted restricted movement and proptosis of his right eye for 3 days and eyelid swelling and pain for 1 day. He had been treated with oral corticosteroids for idiopathic thrombocytopenic purpura in the last month.

Ophthalmologic examination on admission showed no light perception in the right eye. Proptosis, hyperemic and chemotic conjunctiva, and eyelid swelling of the right eye and restricted right eye movement in all directions were confirmed. The right pupil was dilated and unreactive to direct light. The right optic disc was edematous. The left eye was normal. He had a right lower motor neuron seventh cranial nerve palsy. Results of the rest of the neuro-ophthalmologic examination were normal.

The white blood cell count was 12100/mL. Brain CT showed mucosal thickening compatible with inflammation involving the right frontal, bilateral maxillary, sphenoid, and ethmoid sinuses.

Brain MRI was obtained 22 hours after admission. All images were acquired on a 1.5-T instrument (Excite; GE Medical Systems, Milwaukee, Wisconsin). The gradient capacity was 33 mT/m. The following sequences were obtained: precontrast and postcontrast spinecho T1 [time to recovery (TR): 700 ms, time to echo (TE): 8.8 ms, slice thickness 5 mm, inter slice gap 1.5 mm, matrix 288 3 256] and fast spinecho T2 (TR: 4,440 ms, TE: 99.8 ms, slice thickness 5 mm, interslice gap 1.5 mm, matrix 352 3 192) and fluid attenuated inversion recovery (FLAIR) (TR: 8,402 ms, TE: 101.6 ms, time to inversion [TI]: 2,100, slice thickness 5 mm, interslice gap 1.5 mm, matrix 288 3 160). A contrast agent (0.2 mL/kg gadolinium) was administered intravenously. The diffusion sequence (TR: 8,000 ms, TE: 80.8 ms, slice thickness 4 mm, interslice gap 1 mm, matrix 128 3 128) was performed with echo planar single shot spin echo imaging with b values of 0 and 1,000 s/mm². Diffusion gradients were applied in three orthogonal directions to generate three sets of diffusion images (x, y, and z axes). Apparent diffusion coefficient (ADC) values were calculated automatically. A standardized region of interest (ROI) of 2 mm² was used for the measurements. ADC values were calculated from the ROIs by dividing the signal intensity by 1,000 to give values in terms of ADC $3 10^{-3}$ mm²/s. The measurements were from three separate locations on both optic nerves. The mean value was calculated.

The routine MRI sequences were normal. The right optic nerve appeared hyperintense on diffusion imaging and hypointense on the ADC map (Fig. 1A–B). The mean ADC value was 0.471 $3 10^{-3}$ mm²/s for the right optic nerve and 1,663 $3 10^{-3}$ mm²/s for the left optic nerve. The mean diffusion signal value was 315 in the right optic nerve.
FIG. 1. MRI performed 25 hours after vision loss in the right eye. A. Diffusion imaging demonstrates marked diffusion restriction in the right optic nerve (large arrow) and retina (small arrow). B. The apparent diffusion coefficient map shows a corresponding hypointense signal change. C. Postcontrast T1 coronal MRI shows reduced enhancement of the right cavernous sinus (arrows), consistent with thrombosis.

and 133 in the left optic nerve. The mean ADC value was $1.84 \times 10^{-3}$ mm$^2$/s on the right retina and $2.60 \times 10^{-3}$ mm$^2$/s on the left retina. The mean diffusion signal value was 320 on the right retina and 193 on the left retina. The right optic nerve appeared normal on FLAIR and pre- and postcontrast T1 and T2 images. There was right cavernous sinus thrombosis (Fig. 1C). The right superior ophthalmic vein was dilated with heterogeneous intraluminal signal intensity on T2 images. Cerebral magnetic resonance venography showed a normal left superior ophthalmic vein.

On the basis of the clinical and MRI findings, a diagnosis of orbital cellulitis, cavernous sinus thrombosis, and ischemic ocular syndrome was rendered. The patient underwent sinus surgery involving a right maxillary antrostomy, ethmoidectomy, and orbital decompression. There was extensive necrosis and a fungal mass was extracted from the right maxillary sinus. After histopathologic evaluation, the diagnosis was rhino-orbital mucormycosis. Treatment with an antifungal agent along with broad-spectrum antibiotics was started.

On follow-up examination 3 weeks later, left hemiplegia had developed. Brain MRI obtained 20 days after the admission study demonstrated abscesses in the right frontal region (Fig. 2A), prepontine cistern, and corpus callosum

FIG. 2. MRI performed 20 days after the initial study. A. Postcontrast T1 sagittal MRI shows ring enhancement in the frontal lobe (vertical arrow) and frontal and sphenoid sinuses, as well as diffuse enhancement of the genu and body of the corpus callosum (oblique arrow). B. Diffusion imaging shows extensive diffusion restriction in the right cerebral hemisphere, consistent with infarction due to occlusion in the right internal carotid artery. C. Diffusion imaging no longer shows restricted diffusion in the right optic nerve and retina.
and along the tentorium, in addition to extensive right cerebral ischemia due to thrombosis of the right internal carotid artery (Fig. 2B). The restricted diffusion of the right optic nerve and retina had disappeared (Fig. 2C). The patient died 4 weeks after the onset of his illness.

DISCUSSION

At 25 hours after vision loss, our patient had a normal MRI on standard pulse sequences but showed diffusion restriction in the affected optic nerve and retina, as evidenced by a relatively reduced ADC value and diffusion signal intensity. We attribute the restricted diffusion to ischemia caused by occlusion of ophthalmic and central retinal arteries, superior ophthalmic vein, and cavernous sinus due to mucormycosis.

There are some previous reports regarding diffusion imaging in ocular or orbital conditions. The first report (3) was of a 61-year-old patient who experienced bilateral perioperative hypotensive posterior ischemic optic neuropathy after cardiac bypass surgery. The patient was scanned on the fourth day after the onset of symptoms. All sequences except diffusion imaging and FLAIR were normal.

The second report (4) involved a 56-year-old woman with vision loss having features of anterior and posterior ischemic optic neuropathy. Scanned 6 days after vision loss, the patient showed a decrease in ADC value in the diseased optic nerve compared with the unaffected optic nerve.

The third report (5) involved a 44-year-old man who developed bilateral vision loss due to bilateral cavernous sinus and superior ophthalmic vein thrombosis. The proximal ophthalmic arteries were normal on CT. Diffusion imaging demonstrated bilateral optic nerve ischemia. The patient had presented to the hospital 11 days after symptom onset, but there was no information on the timing of the MRI scan. That report was the first to note subtle diffusion restriction in the retina, but the authors did not provide a corroborative retinal ADC value or a follow-up study showing the expected disappearance of restricted diffusion, as we have shown in our patient.

The fourth report (6) involved a 60-year-old woman who developed vision loss due to mucormycosis and subsequent right cavernous sinus thrombophlebitis 15 days after admission (6). The first MRI, performed soon after admission, was normal. The second MRI, performed 6 days after the onset of vision loss in the right eye, revealed subtle diffusion imaging signal abnormality in the affected optic nerve. The diffusion restriction was obvious on the third MRI, performed 15 days after the second study. Other MRI sequences revealed no abnormality. Unlike our very similar patient, there was no mention of diffusion restriction in the retina.

In contrast with the reduced ADC value shown in ischemic optic neuropathy, an increased ADC value has been shown in optic neuritis (7), suggesting that this sequence might be useful in differentiating these two entities.

There are technical limitations to our study. The optic nerve ischemia detected on diffusion images was incidentally depicted on MRI images. Therefore, the image slice was 5 mm and not tailored for the optic nerves. In the future, we recommend using thinner sections (3 mm slice thickness instead of 5 mm) for this purpose. We did not perform coronal or sagittal diffusion imaging because of the unstable condition of the patient. Diffusion imaging near the orbits and skull base tends to show extensive susceptibility artifacts. We tried to overcome this problem by increasing the number of excitations. Although magnetic resonance venography demonstrated the dilatation and heterogeneous signal intensity in the superior ophthalmic vein on the right side, we did not perform CT or MRA to accurately define the arterial supply of the orbital region.

REFERENCES

Restricted Diffusion in the Superior Ophthalmic Vein and Cavernous Sinus in a Case of Cavernous Sinus Thrombosis

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Abstract: A previously healthy 14-year-old boy developed headache, stiff neck, fever, diplopia, right proptosis, and right complete sixth and partial third cranial nerve palsies. Orbital CT showed features of pansinusitis and orbital fat stranding. An initial diagnosis of orbital cellulitis was made. However, closer inspection of the CT disclosed nonfilling of the right superior ophthalmic vein (SOV) and both cavernous sinuses, suggesting cavernous sinus thrombosis (CST). CT venography (CTV) confirmed these features and disclosed nonobstructing thrombus within the left sigmoid sinus and proximal segments of both internal jugular veins. MRI with diffusion imaging disclosed evidence of restricted diffusion within the SOV and cavernous sinuses. These diffusion imaging findings, which may be analogous to those reported with brain parenchymal hematoma, have been described sparingly in intravascular hematoma.

Cavernous sinus thrombosis (CST) is a relatively rare but life-threatening cause of a cavernous sinus syndrome in immunocompetent patients (1). The primary source of sepsis may be a distant focus or contiguous regions (2). The dural sinuses and the cerebral and emissary veins have no valves, allowing blood to flow in either direction according to pressure gradients in the vascular system. This feature, together with the extensive direct and indirect vascular connections of the centrally located cavernous sinuses, makes these structures vulnerable to septic thrombosis from infected tributary sites such as the face, nose, tonsils, soft palate, teeth, and ears. Once antibiotic therapy became widely available, however, the sphenoid sinus emerged as the most common primary source of infection predisposing to CST.

We report a patient who presented with clinical features initially suggesting orbital cellulitis as the primary process. Careful analysis of the clinical and imaging features led to the diagnosis of CST with secondary thrombosis of the right superior ophthalmic vein (SOV) and ipsilateral orbital congestion. We also report MRI evidence of restricted diffusion within the thrombosed cavernous sinuses and SOV, a feature not previously described.

CASE REPORT

A 14-year-old boy developed headache, diplopia, proptosis, and swelling of the right eyelids and redness of the right eye. One day later, he complained of neck pain. His mother noted him to be feverish, confused, and hallucinating. For the preceding 2 days, he had lost appetite and had had a few bouts of vomiting. He complained of marked photophobia.

He had felt weak and had diarrhea for 1 week earlier, manifestations attributed to a “flu-like” illness circulating among family members. His past medical history was unremarkable except for a chronic postnasal drip. Ophthalmologic examination 6 years earlier had been normal.

Emergency room examination disclosed a temperature of 102°F with 80% oxygen saturation, blood pressure of 110/60 mmHg, pulse of 140, and respirations of 20. His neck was stiff. General physical examination findings were otherwise normal.

Ophthalmologic examination was difficult because of the patient’s extreme photophobia and irritability. However, it disclosed normal visual acuity and confrontation visual fields in both eyes. There were no abnormalities of the left eye. There was incomplete right upper lid ptosis and upper and lower eyelid edema with 8 mm of right proptosis but no tenderness to palpation or resistance to retropulsion of the right eye. The conjunctiva of the right eye was mildly hyperemic but not edematous. The right eye was deviated...
inward and could not be abducted beyond the midline. Adduction and infraduction were normal. Supraduction was 50% of normal. The pupils measured 4 mm in dim light and constricted briskly and equally to direct light without afferent defect. Intraocular pressures were 17 mmHg in the right eye and 14 mmHg in the left eye. Portable slit-lamp examination was normal and ophthalmoscopy showed clear media and no abnormalities of the retina or optic nerves. Neurologic examination disclosed that the patient was disoriented to time and place, irritable, and inattentive. There were no focal deficits apart from those affecting the eyes.

Postcontrast CT of the orbits showed right proptosis and “fat stranding” in the right orbit (Fig. 1A–B). The right superior ophthalmic vein (SOV) was enlarged and did not enhance normally, suggesting thrombosis. Poor contrast enhancement was noted within both cavernous sinuses (right more than left). The maxillary, ethmoid, frontal, and sphenoid sinuses showed mucosal thickening, and there was an air-fluid level in the frontal sinuses.

The initial emergency room diagnosis was orbital cellulitis. However, the ophthalmic findings of complete right sixth cranial nerve palsy and superior division right third cranial nerve palsy, together with the orbital CT findings, were more consistent with a retro-orbital (cavernous sinus) than with an orbital process.

Hemoglobin was 11.2 g, white cell count was 18,300 with neutrophil predominance, and standard chemistry results were normal, including hepatic and renal panels and urinalysis. Lumbar puncture without a recording of opening pressure disclosed protein of 142 mg/dL, glucose of 42 mg/dL (serum glucose of 100 mg/dL), red cell count of 2,037, white cell count of 303 (neutrophils 65%), and a negative Gram stain. Blood and spinal fluid culture results were negative.

CT venography (CTV) did not show the expected contrast opacification of the right cavernous sinus and showed only minimal contrast opacification of the anterior aspect of the left cavernous sinus (Fig. 2A–B). There was mass effect with narrowing of cavernous segments of both internal carotid arteries. The right SOV was enlarged and showed no contrast (Fig. 2C). The left SOV was normal. There was also no contrast within the left superior petrosal sinus (Fig. 2D), and there were nonobstructive filling defects within the left sigmoid sinus (Fig. 2E) and proximal segments of both internal jugular veins (Fig. 2F).

MRI of the brain and orbits was performed 1 day later with a 3.0-T Achieva magnetic resonance system (Philips Medical Systems, Best, The Netherlands) using an 8-channel SENSE head coil. Diffusion imaging data were obtained using an echo-planar single-shot technique with the shortest TR, 49 ms TE and a 90 flip angle, and a b value of 1,000 seconds/mm². The data were recorded on a 128 x 128 matrix and were zero-filled for a final resolution of 128 x 256. Axial slices with 4-mm slice thickness and a 1-mm interslice gap were obtained. A SENSE P factor of 3 was used. The total imaging time was 49 seconds.

MRI confirmed the CT findings. T2 (Fig. 3A) and precontrast T1 (Fig. 3B) images showed heterogeneous signal within these regions. On postcontrast T1 images, there were filling defects within both cavernous sinuses. There was also extensive thickening and enhancement of the walls of the cavernous sinuses, adjacent tentorium (Fig. 3C), and dural lining of the cerebral hemispheres. The dural enhancement was attributed to reactive dural congestion or changes due to recent lumbar puncture. Diffusion images revealed high signal and corresponding apparent
coefficient diffusion (ADC) low signal within both cavernous sinuses (Fig. 4A–B) and the right SOV (Fig. 4C–D). These diffusion abnormalities were attributed to thrombosis.

When added to the clinical findings, these imaging findings led to a change in diagnosis from orbital cellulitis to sphenoid sinusitis causing CST and meningitis with secondary SOV thrombosis and right orbital congestion. The signal abnormalities in the jugular and left sigmoid sinuses were believed to represent propagated clot from the cavernous sinuses.

The patient was treated with intravenous 10 mg/kg vancomycin every 6 hours, 4 g piperacillin/tazobactam...
FIG. 4. A, B. Both cavernous sinuses show hyperintensity (A, arrows) with corresponding apparent diffusion coefficient (ADC) hypointensity (B, arrows). C, D. The anterior segment of the right superior ophthalmic vein (SOV) shows hyperintensity (C, bracketed by arrows) with corresponding ADC hypointensity (D, bracketed by arrows). These signal abnormalities reflect restricted diffusion owing to thrombosis.

every 6 hours, and 5 mg/kg metronidazole every 6 hours and heparin (later enoxaparin). Within 2 days, his mental status had normalized and the lid edema, ptosis, and supraduction deficit had improved. All other ophthalmic findings persisted at discharge 1 week after admission.

Follow-up brain MRI after 3 months showed interval improvement in the right cavernous sinus opacification. There was, however, some residual narrowing of the right internal carotid artery and the right SOV still did not show complete opacification. The diffusion images were not reliable as the follow-up examination was performed on the MRI sequence without parallel imaging.

DISCUSSION
Our patient had typical clinical and imaging features of CST, but bacterial orbital cellulitis spreading from adjacent ethmoid sinusitis was the initial diagnosis because unilateral proptosis and ptosis in a young patient are much more likely to represent this process. It was only after we carefully analyzed the clinical and full imaging features that we determined the diagnosis of CST. Absent abduction and impaired supraduction and ptosis in the presence of spared adduction and infraduction favored a retro-orbital rather than an orbital process. The lack of contrast opacification in both cavernous sinuses, the right SOV, and the left superior petrosal sinus, together with filling defects in the sigmoid sinuses and internal jugular veins, confirmed that CST was the cause of the proptosis. The imaging evidence of bilateral CST, even when clinical manifestations are limited to one side, is consistent with previous reports demonstrating up to 75% incidence of bilateral imaging findings with unilateral clinical presentations (3).
Although CT imaging provides ample evidence of CST, MRI is critical for evaluation of potential complications of CST such as intracranial dissemination of infection or cerebral infarction. In our patient, MRI also unexpectedly revealed abnormalities on diffusion imaging that have not been previously described in CST or in any cases of intravascular thrombosis in the head and neck. Although restricted diffusion has been described within the optic nerve owing to venous ischemia from CST (4–6), restricted diffusion within the SOV and cavernous sinuses was not mentioned in those reports.

Diffusion imaging is a relatively new technique for evaluating the diffusion properties of tissue water molecules and has been used widely to study ischemia, tumors, infections, and white matter disorders (7,8). There are few reports of its use in lesions of the skull base and orbits, perhaps because these regions contain inhomogeneous tissues (bone, air, fat, and soft tissue) that produce severe susceptibility artifacts (9). Wider availability and application of sensitivity encoding (SENSE), the technique we applied, may enhance the quality of echo-planar diffusion imaging by reducing the blurring and off-resonance artifacts at the skull base and posterior fossa (9).

Diffusion imaging has been evaluated previously for intraparenchymal brain hematoma, for which it produces a variety of signal abnormalities depending on the stage of the hematoma (10,11). In the hyperacute stage, the diffusion imaging signal is high owing to restricted diffusion from shrinkage of the extracellular space caused by clot retraction, plasma resorption, and conformational changes in the hemoglobin molecule. In the acute, early subacute, and chronic stages, the diffusion imaging signal is hypointense owing to magnetic inhomogeneity from intracellular deoxyhemoglobin (acute stage), paramagnetic intracellular methemoglobin (subacute stage), and hemosiderin (chronic stage). Because a susceptibility artifact from this inhomogeneity causes marked diffusion imaging hypointensity, ADC measurements in these stages cannot be reliably calculated (7,11). The only exception to the uniform hypointense signal in these periods occurs in the late subacute stage, in which red blood cell lysis, distribution of intracellular contents in the extracellular space, and high viscosity from inflammatory cell and macrophage infiltration may contribute to restricted diffusion and diffusion imaging hyperintensity (11).

Favrole et al (12) reported restricted diffusion within intravascular clots in 12 (41%) of 28 patients with cerebral venous thrombosis on MRI examination performed between 1 and 30 days after clinical onset. None of their cases involved the cavernous sinus or superior ophthalmic veins. Moreover, they did not attempt to date the thrombus based on the diffusion imaging findings. Our patient demonstrated mostly a very high diffusion imaging signal, which should correspond to the hyperacute stage of brain parenchymal hematoma. Yet the diffusion imaging study was performed several days into his illness. Perhaps intravascular thrombi do not undergo the evolutionary stages described for intraparenchymal hematoma. We have seen similarly high diffusion imaging signal abnormalities well after the hyperacute stage in intramural hematoma in arterial dissection (unpublished data) and as recently reported by Choi et al (13).

Our report suggests that diffusion imaging may be helpful in the diagnosis of cavernous sinus and superior ophthalmic vein thrombosis. The absence of restricted diffusion, however, should not exclude the diagnosis. Correlation of clinical signs with conventional imaging signs remains important in this regard. Further studies of diffusion imaging signal abnormalities in patients with intravascular thrombosis and arterial and venous hematomas will be helpful to validate our findings.

REFERENCES

Direct Carotid-Cavernous Fistula Causing Brainstem Venous Congestion

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Abstract: A 39-year-old man who presented with unilateral proptosis and periocular pain rapidly developed reduced consciousness, facial numbness, dysarthria, and gait ataxia from a direct carotid-cavernous fistula (CCF) with drainage into posterior fossa veins. Brain MRI revealed abnormal signal throughout the brainstem, indicative of venous hypertension and edema. Closure of the fistula by detachable balloon eliminated the clinical and imaging abnormalities. This is the fifth reported case of brainstem complications of a direct CCF. It highlights potentially serious complications of this condition and their reversibility with prompt treatment.

(C)arotid cavernous fistulas (CCFs) are acquired lesions caused by aberrant communication between the internal or external carotid arteries and the cavernous sinus (1,2). Patients classically present with the clinical triad of proptosis, chemosis, and pulsatile bruises and less commonly with ophthalmoplegia, visual loss, and facial pain. We describe a patient with a CCF who presented with signs of anterior (orbital) venous congestion and who went on to develop neurologic signs of posterior (brainstem) drainage.

CASE REPORT

A 39-year-old man developed sudden left-sided headache and pulsatile tinnitus followed by left periocular pain, left eye proptosis, and horizontal diplopia. There was no history of trauma. Our examination disclosed visual acuities of 20/20 in the right eye and 20/150 in the left eye. Intraocular pressures were normal as were pupil size and reactivity, visual fields, and ophthalmoscopy. He had a left abduction deficit consistent with a left sixth cranial nerve palsy. Head CT suggested a left CCF based on enlargement of the superior ophthalmic veins bilaterally and prominence of the cavernous sinuses, with the left greater than the right.

Over the next 24 hours, he developed severe left proptosis, chemosis, and ophthalmoplegia, and visual acuity in the left eye deteriorated to only light perception (Fig. 1A). He became drowsy and developed left facial numbness, marked dysarthria, and gait ataxia.

Brain MRI revealed findings consistent with a left CCF, as well as diffuse T2 signal hyperintensity in the brainstem (Fig. 2A) and enhancement of the left basis pontis (Fig. 2B).

An urgent cerebral angiogram confirmed a direct high-flow left CCF with robust filling of the cavernous sinuses and ophthalmic veins bilaterally (Fig. 3A). Abnormal early venous contrast filling of posterior fossa veins was visible (Fig. 3B). Significant tortuosity and ectasia of both carotid and vertebral arteries and intracranial vessels was evident, suggesting an underlying connective tissue abnormality.

Near complete obliteration of the fistula was achieved with a single detachable latex balloon placed directly into the fistula, maintaining patency of the internal carotid artery (Fig. 3C). Although a small residual shunt was present at the end of the procedure (Fig. 3C), the proptosis and chemosis had completely resolved at 6 months follow-up (Fig. 1C). Visual acuity had recovered to 20/25 bilaterally, and eye movements were normal. Speech and coordination had normalized. Brain MRI at 1 year follow-up demonstrated complete resolution of the abnormal signal observed in the brainstem (Fig. 2C).

DISCUSSION

The clinical presentation of CCFs depends on the degree of shunting and the route of venous drainage (1,2). Under normal conditions the cavernous sinus receives drainage anteriorly from the superior and inferior ophthalmic veins and superiorly from the sphenoparietal sinus and cortical veins. Blood flow into the cavernous sinus drains posteriorly into the inferior and superior petrosal sinuses...
FIG. 1. A. Before treatment of the fistula, our patient shows left eye proptosis and chemosis and conjunctival chemosis. B. Three days after treatment, the proptosis and chemosis are reduced. C. Six months after treatment, all signs have disappeared.

and inferiorly into the pterygoid plexus. The shunt created by CCFs causes increased blood flow through normal drainage pathways and may cause reversal of flow into tributaries such as the ophthalmic veins. Rarely, reflux into cortical veins may occur, which can lead to focal hemispheric signs, seizures, venous infarction, or intracranial hemorrhage (1,2).

We have described a patient with venous congestion of the brainstem due to a direct CCF. Four such patients have been reported previously (3–5). There have been several additional reports of patients with indirect CCFs presenting with brainstem venous congestion (6–12). Increased shunting of blood into the petrosal system, which also drains the brainstem, is hypothesized to cause venous hypertension and edema formation in the brainstem. Alternatively, thrombosis of dural sinuses or veins of the posterior fossa may cause increased venous congestion. Kai et al. (7) have speculated that contrast-enhancing brainstem lesions in patients with CCFs may indicate irreversible damage. Clearly, these changes can be reversible, however, as illustrated by our patient and the patient reported by Iwasaki et al. (6).

Brainstem venous congestion is a rare but potentially serious complication of CCFs. Recognition of symptoms, signs, and radiographic findings associated with this complication warrants urgent investigation and definitive treatment to achieve the best possible patient outcome.
FIG. 2. Brain MRI. A. Coronal FLAIR study demonstrates increased signal diffusely in the brain stem (arrows). B. Postcontrast T1 coronal study demonstrates enhancement of the left side of the pons (arrow). C. Coronal FLAIR study demonstrates complete resolution of the abnormal signal at 1 year follow-up.
FIG. 3. Left common carotid cerebral arteriogram. A. Anterior-posterior (left) and lateral (right) views demonstrate the left-sided direct carotid-cavernous fistula (arrows). B. Anterior-posterior (left) and lateral (right) views demonstrate abnormal early venous contrast filling of posterior fossa veins. (1. Peduncular veins, 2. Anterior pontomesencephalic vein, 3. Median anterior medullary vein, 4. Vein of cerebello-pontine fissure, 5. Median spinal vein, 6. Cilval plexus.) C. Anterior-posterior (left) and lateral (right) views after balloon detachment demonstrate near complete occlusion of the fistula. The faint outline of the balloon can be discerned at the prior site of the fistula (arrows).
Acknowledgment

The photograph for Figure 1A was provided by Dr. A. Pirbhai.

REFERENCES

Gaze-Evoked and Rebound Nystagmus in a Case of Migrainous Vertigo

Sun-Young Oh, MD, Man-Wook Seo, MD, Young-Hyun Kim, MD, Kwang-Dong Choi, MD, Dae-Seong Kim, MD, and Byoung-Soo Shin, MD

Abstract: A patient with migrainous vertigo showed pronounced gaze-evoked and rebound nystagmus during an attack. These findings, which have not been previously documented, suggest that migrainous vertigo is based on central vestibular dysfunction.

Migrainous vertigo (MV) is an increasingly recognized cause of episodic vertigo and headache (1). However, whether MV is a central or peripheral vestibular system disorder is not known. As in any paroxysmal disorder, the physical examination during the acute episode is indispensable for an understanding of the underlying pathophysiology. We present a patient with MV who showed pronounced gaze-evoked and rebound nystagmus together with gait imbalance during an attack, suggesting that central vestibular dysfunction was the basis of the clinical manifestations.

CASE REPORT

A 57-year-old woman had episodes of severe headache, nausea and vomiting, and a slight imbalance almost always associated with vertigo. She also experienced isolated incidents of spontaneous vertigo without headache and migraine-like headache without vertigo.

The headache and vertigo attacks lasted from 30 minutes to several days and had occurred once or twice per month for more than 10 years. The headache was pulsating and hemicranial. It alternated sides and was associated with nausea, vomiting, and rarely photophobia and phonophobia. The vertigo was aggravated by body position changes.

She had no family history of migraine, vertigo, or episodes of ataxia. Various analgesics had not provided alleviation of symptoms. Results of several electroencephalograms had been normal as were results of hematologic examinations, including a complete blood cell count, electrolytes, glucose, erythrocyte sedimentation rate, and liver and kidney function tests.

During an episode, gaze-evoked nystagmus (GEN) and rebound nystagmus were captured on video (see Supplemental Digital Content 1, http://links.lww.com/A685) and in three-dimensional oculography (Fig. 1) in eccentric positions of gaze under lighted conditions in the horizontal (30–35) plane. In the vertical (25–30) plane and after the patient’s symptoms had resolved, GEN and rebound nystagmus were not observed.

Although she showed normal findings on finger-to-nose, heel-to-shin, and diadochokinesis tests, we observed disturbed stance and gait during the attack. She could stand and walk with eyes open but could not stand with eyes closed. She was unable to perform a tandem gait. (This impaired gait and balance normalized 2 days later.)

During the attack, findings from the rest of the neurologic examination, calorics, bedside head-thrust tests, and audiometry were unremarkable. Results of brain MRI and fluorodeoxyglucose positron emission tomography (FDG-PET) were also normal. (Fig. 2).

To exclude the diagnosis of episodic ataxia type 2 (EA-2), we performed a polymerase chain reaction (PCR)-based direct sequence analysis of all coding regions of CACNA1A. Genomic DNA was extracted from the patient’s peripheral blood and was amplified using 52 primer pairs covering 47 exons and their neighboring intron sequences (2). The amplified products from the PCR reaction were then separated on 2% agarose gels, purified, cycle-sequenced with PCR primers using a BigDye Terminator Sequencing Kit (PE Applied Biosystems, Foster City, CA), and electrophoresed using an ABI PRISM 3730XL DNA analyzer (PE Applied Biosystems). By visual analysis of
FIG. 1. Gaze-evoked nystagmus recorded by three-dimensional oculography during an episode of headache, vertigo, and gait imbalance. The eyes were tested under lighted conditions in the horizontal (30°) plane.

gel electrophoresis of amplified PCR products and chromatograms, we were able to exclude a mutation of CACNA1A, including an abnormal CAG expansion at exon 47.

A diagnosis of MV was made, and the patient was treated abortively with oral sumatriptan and prophylactically with 80 mg/day propranolol and 50 mg/day topiramate. Symptoms improved several days later. On examination 6 months after discharge, the patient reported only one attack of headache of relatively decreased intensity.

DISCUSSION
Our patient experienced episodic spontaneous or positional vertigo with imbalance aggravated by head and body movements. She also experienced migraine according to the criteria of the International Headache Society (3),

FIG. 2. Normal appearance of brainstem and cerebellum on axial T2 MRI (A) and [18F]fluorodeoxyglucose positron emission tomography (B) performed during the episode described in Figure 1.
including nausea, vomiting, and photophobia accompanied by vertigo. After appropriate investigations ruled out other causes of her symptoms, we settled on a diagnosis of MV based on the criteria proposed by Neuhauser et al (4).

The principal alternative diagnoses in our patient are basilar migraine and transient ischemic attacks. To fulfill the diagnosis of basilar migraine, she would have needed at least two of the following symptoms: dysarthria, diplopia, and ataxia, which she lacked (5). We excluded transient ischemic attacks because she had had attacks for 10 years without other neurologic manifestations and with normal brain imaging.

Between attacks of MV, various ocular motor signs have been reported (1, 6-8), including saccadic pursuit, spontaneous or positional nystagmus, vertical nystagmus, GEN, and impaired fixation suppression of vestibulo-ocular reflex (VOR) (1, 8). During attacks of MV, there are only a few reports of ocular motor findings (8-10), including spontaneous and positional nystagmus, saccadic pursuit, caloric weakness, and gait ataxia (9). In one report, two patients with MV showed very mild GEN during the acute episode (10). Our patient showed pronounced GEN and rebound nystagmus during an acute episode of MV. These findings suggest a central vestibular origin of MV.

GEN is caused by an inadequately sustained eye position signal originating from the neural integrator. This form of nystagmus is associated with cerebellar disorders involving the vestibulocerebellum (flocculonodular lobe) or its connections (11, 12) and brainstem lesions affecting the nucleus prepositus hypoglossi (NPH) and medial vestibular nucleus (MVN) (2). Rebound nystagmus is most often encountered in patients with cerebellar lesions involving the flocculus and paraflocculus (13), and it also occurs in monkeys with lesions in the flocculus and paraflocculus (11) and with bilateral lesions restricted to the NPH and MVN (14).

The calcium channel gene has been considered a candidate in MV (15, 16). This hypothesis relies on findings of involvement of the CACNA1A gene region in some families with non-hemiplegic migraine with and without aura (17). Mutations in the CACNA1A gene of a neuronal Ca2+ channel have been identified in familial hemiplegic migraine (FHM), EA-2, and spinocerebellar ataxia type 6. No such mutations have been found in basilar hemiplegic migraine (FHM), EA-2, and spinocerebellar ataxia type 6. No such mutations have been found in basilar migraine and transient ischemic attacks, which are involved in the initiation of migraine attacks. The vestibular nuclei receive fibers from these structures (18-20). Our lack of apparent brainstem or cerebellar activation might be related to the use of FDG-PET rather than H2 15 O-PET in the study of our patient. FDG-PET may not be sufficiently sensitive to pick up changes in brainstem activity during migraine attacks.

Recently, PET with radioactive water (H2 15 O) performed during acute migraine attacks has identified activation of the locus ceruleus and the dorsal raphe nucleus, which are involved in the initiation of migraine attacks. The vestibular nuclei receive fibers from these structures (18-20). Our lack of apparent brainstem or cerebellar activation might be related to the use of FDG-PET rather than H2 15 O-PET in the study of our patient. FDG-PET may not be sufficiently sensitive to pick up changes in brainstem activity during migraine attacks.

REFERENCES
Temporary Adduction Deficit After Nasal Septoplasty and Radiofrequency Ablation of the Inferior Turbinate

Saeid Atighechi, MD, S. Hossein Alimohammadi, MD, Mohammad Hossein Baradaranfar, MD, and S. Abbas Mirvakili, MD

Abstract: A 19-year-old boy developed an adduction deficit after bilateral radiofrequency ablation of the inferior turbinate and septoplasty. Postoperative imaging disclosed an intact medial orbital wall and high T2 signal and enlargement of the medial rectus. Within 3 months, the motility deficit had resolved. This manifestation is attributed to injury of the medial rectus from radiofrequency ablation and represents the first reported case.


Septoplasty and radiofrequency ablation of the inferior turbinate are common procedures in the management of patients with nasal obstruction due to septal deviation and hypertrophy of the inferior turbinate (1). Ophthalmic complications of these procedures are rare (2–7). We report a patient with temporary postoperative diplopia due to medial rectus paresis.

CASE REPORT

A 19-year-old boy had symptoms of nasal obstruction owing to septal deviation and bilateral hypertrophy of the inferior turbinate and reduced air flow, especially on the right (Fig. 1).

Septoplasty was performed under general anesthesia with a hemi-transfix incision on the left side of the nasal septum. When the procedure was finished, the mucoperichondrial flap was completely intact. With a bipolar radiofrequency probe at 10-watt power, the inferior turbinate was treated under standard protocol. No intraoperative complications were noted. Upon awakening from anesthesia, the patient reported diplopia. Limited adduction of the right eye and swelling of the inferior right eyelid were noted (Fig. 2).

Ophthalmologic consultation disclosed a visual acuity of 20/20 bilaterally, confirmed the ocular motility and eyelid findings, and found normal pupillary function and direct ophthalmoscopy.

Postoperative CT with 2-mm thickness and 3-mm intervals and MRI of the orbit and brain with 3-mm sections were performed on the second and third postoperative days, respectively. They did not disclose any abnormalities except edema of the right orbit, inflammation in the right anterior ethmoid cells, and high-intensity T2 MRI signal and enlargement of the right medial rectus. The medial wall of the orbit was intact (Figs. 3 and 4).

The patient was treated with 1 mg/kg/day prednisolone orally. On the fourth postoperative day, swelling of the eyelid was improved, and diplopia in primary gaze position was minimally improved. The patient was discharged with a tapering schedule of oral prednisolone. Within 3 months of surgery, ocular motility had returned to normal (Fig. 5).

FIG. 1. Preoperative precontrast coronal CT shows rightward septal deviation and hypertrophy of the inferior turbinates.
FIG. 2. Our patient’s ocular motility on the first postoperative day shows a right exodeviation and a complete right adduction deficit. Top, primary position; middle, right gaze; bottom, left gaze.

DISCUSSION

Our patient had temporary dysfunction of the medial rectus after standard nasal septoplasty and radiofrequency ablation of the inferior turbinate.

The anatomic proximity of the orbit to the adjacent sinus and nose exposes the orbital contents to trauma in sinus and nose surgery (2–7). Huang et al (8) divided injury to the medial rectus into four patterns, particularly with reference to the degree of direct injury (mainly the degree of muscle tissue loss). Pattern I was applied to muscle transection, pattern II to partial muscle transection, pattern III to a contused, entrapped muscle, and pattern IV to a contused muscle without entrapment. Our patient fits pattern IV, but unlike the patients of Huang et al (8), the orbital wall in our patient was intact.

Two patients with ocular motility disorders without orbital wall damage have been previously reported (6,9). Kosko et al (6) described a patient with unilateral partial third nerve palsy after bilateral sinus surgery. The diplopia and anisocoria resolved 2 months after the surgery. They suggested that this complication resulted from postoperative edema (6). Bayramlar et al (9) reported temporary hypertropia, supraduction deficit, ipsilateral mydriasis, and accommodative paresis after bilateral endoscopic ethmoidectomy, bilateral partial inferior turbinectomy, and septoplasty.

FIG. 3. Precontrast axial CT performed on the second postoperative day shows an intact right lamina papyracea and continuity of the right medial rectus. There are postoperative changes within the right anterior ethmoid air cells.
FIG. 4. Axial T2 MRI performed on the third postoperative day shows enlargement and high signal within the right medial rectus.

but without radiofrequency ablation in a Caldwell-Luc approach for chronic sinusitis. In their patient, all of these manifestations resolved within 2 months (9).

The medial rectus dysfunction in our patient probably resulted from the radiofrequency ablation. In their review of 1,600 patients who underwent percutaneous radiofrequency trigeminal rhizotomy, Kanpolat et al (10) noted transient sixth cranial nerve palsy in 11 patients and transient third cranial nerve palsy in 2 patients. Two patients had permanent sixth cranial nerve palsy. The proposed mechanisms of the side effects or complications of percutaneous radiofrequency rhizotomy are mislocation of the electrode and spread of thermal energy to neighboring neural structures (11). We have encountered

FIG. 5. Three months after surgery, the patient has full ocular ductions and normal ocular alignment.
no previous reports of similar injury to the medial rectus or any other extraocular muscle after radiofrequency ablation in nasal or sinus surgery. There is one report (12) of irreversible blindness in one eye and impairment of the infratemporal visual field in the other eye after electrocoagulation performed for delayed bleeding after functional endoscopic sinus surgery. These complications were attributed to expansion of thermal energy to neighboring neural structures.

Postoperative imaging in our patient did not demonstrate orbital or intracranial abnormalities except edema of the medial rectus muscle and anterior ethmoid air cells. In such circumstances, the patient can be reassured that the deficits are transient and that complete recovery may be anticipated within months.

REFERENCES
Pupil Perimetry Demonstrates Hemifield Pupillary Hypokinesia in a Patient With a Pretectal Lesion Causing a Relative Afferent Pupil Defect but No Visual Field Loss

Eleni Papageorgiou, MD, Thomas Wermund, MD, and Helmut Wilhelm, MD

Background: Lesions affecting the pretectum or the brachium of the superior colliculus (brachium) and sparing the optic tract cause a contralateral relative afferent pupil defect (RAPD) but no visual field loss. It has been assumed that the pupillomotor pathways within the brachium are a continuation of the pupillomotor pathways traveling in the optic tract. To investigate this assumption, we looked for hemihypokinesia by means of pupil perimetry.

Methods: Pupillary hemifield stimulation was performed in a 65-year-old woman with normal visual fields and an isolated left RAPD due to a cerebral hemorrhage affecting the right dorsal midbrain. The pupil responses from light stimulation of the nasal inferior, nasal superior, and temporal inferior and temporal superior quadrants of both eyes were recorded using computerized binocular infrared pupillography. Each stimulus was presented 5 times and the mean amplitude of the pupil response was calculated for each stimulus location.

Results: Pupil perimetry demonstrated a marked hemihypokinesia (reduced light reaction) in the hemifield contralateral to the site of the lesion.

Conclusions: Our experiment suggests that the brachium is indeed a continuation of the afferent pupillary fibers traveling in the optic tract.


Methods

Patient Features

In January 2006, a 65-year-old woman developed acute headache, dysphagia, heaviness of the left arm and leg, and numbness on the left side of the body. There was a history of increased blood pressure and hyperlipidemia. Neurologic examination showed mild hemiparesis of the
left arm and leg, a left hemisensory deficit, and a right gaze palsy. Cranial CT demonstrated a hemorrhage in the right basal ganglia, which also involved the right posterior thalamus and the right dorsal midbrain (Fig. 1). It appeared to spare the right optic tract.

Seven months after clinical onset, all of the patient’s neurologic manifestations had resolved except a left hemisensory deficit. She did not report any visual difficulties. Visual acuity was 20/20 in both eyes with normal color vision and full visual fields as assessed with Octopus 101 static automated perimetry. Results of slit-lamp and ophthalmoscopic examinations were unremarkable, and ocular motility was normal in both eyes. The pupils were of equal size, but there was a left RAPD of 0.9 log unit by neutral density filters and 1.33 log units by an automated pupillographic swinging flashlight test.

Pupil Perimetry
We performed pupil perimetry using light stimuli (circles) of 12 diameter and 8 cd/m² luminance presented on a 19-inch computer monitor under mesopic conditions (background luminance of 1 cd/m²). A custom-built prototype was used to provide the hemifield stimuli on the monitor and to record simultaneously the right and left horizontal pupil diameters at 25 times per second. All parameters concerning pupil perimetry are listed in Table 1.

We used one stimulus in each quadrant (Fig. 2). Each stimulus was presented 5 times, and the mean amplitude of the pupil response was calculated for each stimulus location using computer software. In accordance with the methods of Kardon et al (6), the term “hemifield” is used to refer to the corresponding visual field side.

RESULTS
Based on the mean amplitudes of the pupil responses in each quadrant (Table 2), a pupillary hemihypokinesia was present with loss of pupillomotor sensitivity contralateral to the side of the lesion. The mean amplitudes of the pupil responses in the left hemifields were very low in both eyes, reflecting a homonymous pattern of pupillomotor sensitivity loss contralateral to the optic tract lesion (Fig. 2).

The pupil response from the functioning temporal hemifield ipsilateral to the tract lesion (right eye) was greater than that from the functioning nasal hemifield contralateral to the tract lesion (left eye).

DISCUSSION
The pupil light reflex in isolated pretectal lesions provides a unique model for selectively studying the pupillary pathway anatomy because the afferent pupillomotor fibers here are anatomically separate from the visual fibers.

The clinical findings in the present patient are consistent with a lesion that selectively damaged the pupillary afferents in the brachium or its destination in the pretectal nucleus. Although our patient had a relatively large hemorrhage, the absence of a homonymous field defect excludes a substantial lesion of the optic tract. In addition, the normal color of the optic disc proves that the optic tract is not involved.

<table>
<thead>
<tr>
<th>TABLE 1. Instrumentation and stimulus characteristics used in pupil perimetry</th>
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<tr>
<td>Campimetry monitor</td>
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<tr>
<td>Testing distance</td>
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<tr>
<td>Visual field covered</td>
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<tr>
<td>Stimulus size</td>
</tr>
<tr>
<td>Stimulus luminance</td>
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<tr>
<td>Pupillography</td>
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<tr>
<td>Data analysis</td>
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</tbody>
</table>
FIG. 2. Pupil perimetry results. The black circle between 10 and 20 in each quadrant indicates the position of the presented stimuli (12 diameter, 8 cd/m² brightness). Note the marked hemihypokinesia in the left hemifield of both eyes as well as the difference in pupil response between the functioning (temporal) hemifield of the right eye and that of the left eye (nasal), which represents the intereye difference observed clinically (left RAPD).

Lesions confined to this anatomic region are rare and may often remain undetected, as they are not accompanied by a visual deficit. Behr (7) first described a RAPD in two patients with no detectable visual dysfunction after stroke. He proposed that the lesion involved the afferent pupillary pathway in the brachium or pretectum (7). Nine such cases indicating affection of the brachium or the pretectum were subsequently published between 1984 and 2005 (2–5,8–12). The majority of the reported patients manifested additional neurological signs and accompanying ocular motility disorders, as did our patient. The underlying pathologic lesion in the reported cases was tumor, hemorrhage, or infarction in the dorsal midbrain and the RAPD was, as in our patient, always contralateral to the lesion (2–5,7–12).

The pupillary hemihypokinesia we found in our patient represents the pupillographic correlate of the clinically observed contralateral RAPD. These results are identical to those we would expect in an optic tract lesion. Consequently, the RAPD in isolated unilateral pretectal lesions has the same origin as the RAPD in optic tract lesions, which primarily represents a difference in light sensitivity between the intact nasal and temporal hemiretinas (6). Even in retrogeniculate lesions, a contralateral RAPD may be observed (13,14). There are strong hints that even in those cases the lesion involves the brachium of the dorsal midbrain. Our findings suggest that there is no need to posit a cortico-pretectal pathway to account for the RAPD in brachium or pretectal lesions, which may play a role in other pupillary phenomena (15).

### TABLE 2. Contraction amplitude values of the pupil response in each of the four quadrants

<table>
<thead>
<tr>
<th></th>
<th>Left Eye</th>
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<th>Right Eye</th>
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<tr>
<td></td>
<td>Mean amplitude (mm)</td>
<td>SD</td>
<td>Mean amplitude (mm)</td>
<td>SD</td>
</tr>
<tr>
<td>Inferior temporal</td>
<td>0.18</td>
<td>0.03</td>
<td>1.20</td>
<td>0.04</td>
</tr>
<tr>
<td>Inferior nasal</td>
<td>0.62</td>
<td>0.04</td>
<td>0.50</td>
<td>0.06</td>
</tr>
<tr>
<td>Superior nasal</td>
<td>0.42</td>
<td>0.06</td>
<td>0.41</td>
<td>0.10</td>
</tr>
<tr>
<td>Superior temporal</td>
<td>0.18</td>
<td>0.06</td>
<td>1.17</td>
<td>0.17</td>
</tr>
</tbody>
</table>

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In the adult cerebral cortex, cortical remapping has been found after altered inputs in normal subjects (1, 2) and in patients with retinal (3) and cortical lesions (4). Reorganization after peripheral or central visual deafferentation alters visual perception mainly by filling in the impaired visual field with information derived from areas neighboring the scotoma (4, 5) and by generating spatial distortion (5, 6). However, it is not yet clear whether such cortical reorganization affects perception and impinges on areas remote from the scotoma.

There is evidence in normal subjects and patients that perceptual alterations can occur at some distance from scotoma borders. In normal subjects, Ramachandran and Gregory (2) reported that when a cross made of two lines of different length fell on the physiologic blind spot, only the longer one appeared continuous. Kapadia et al (1) induced an artificial scotoma in normal individuals and observed a perceptual shift that pulled the perceived images surrounding the scotoma by a few minutes of arc toward the center of the masked area. The shift increased with eccentricity from the fixation point. These observations suggest that cortical reorganization can involve visual information functionally related to areas distant from the scotoma.

In a previous clinical report (6), we described patients with homonymous paracentral scotomas who perceived one of their interlocutor’s elbows as being narrower than it actually was. We named this form of perceptual spatial distortion the “thin man phenomenon.” To explore the nature of this phenomenon, we devised a test that we named the “parallel line test.” It consists of asking subjects to fixate a point located between two isometric vertical parallel lines, one of which crosses the scotoma, and to describe any perceived alteration on a displayed figure. Patients with homonymous paracentral scotomas perceived the line crossing the scotoma as being shorter than the mirrored one. The effect of distance from the scotoma border on perceptual distortion was not explored.

The purpose of the present study was to investigate whether spatial distortion occurs only in the vicinity of scotoma borders or also in more distant areas of the visual field.
field and whether spatial distortion varies as a function of the distance from the scotoma border.

This investigation was performed in patients with homonymous paracentral scotomas, as they are able to fixate centrally, hence preventing the occurrence of possible perceptual bias and instability induced by eccentric fixation. Moreover, proximity of the fixation point to the visual field defect facilitates the analysis of scotoma-induced perceptual distortion. In addition, selecting patients with cortical rather than retinal lesions prevents interference from metamorphopsias generated by retinal tissue deformation. In our previous investigation (6), we found that the parallel line test was suitable to evaluate perceptual alterations in patients with homonymous paracentral scotomas and we therefore tailored this test to this investigation.

METHODS

Patients

Two patients were included in the study.

The first patient (NG) was a 60-year-old woman who had had an ischemic injury in the left occipital lobe 11 years earlier, resulting in an inferior right homonymous paracentral scotoma (Fig. 1 and Fig. 2) (6). No major changes were noted when her clinical assessment was repeated.

The second patient (CS) was a 53-year-old woman who had attempted suicide 6 months earlier by injecting 100 mg morphine and 45 mg midazolam intravenously. She was found at a Glasgow Coma Scale score of 3 and referred to the intensive care unit. Brain CT and MRI performed a few hours later showed an ischemic lesion in the left occipital lobe (Figs. 1 and 2). The attempt presumably provoked an episode of reduced blood pressure, which affected the occipital watershed area (7), resulting in a right inferior homonymous paracentral scotoma.

After explanation of the nature and possible consequences of the study, patients gave their informed consent in accordance with the Declaration of Helsinki for research with human subjects.

Experimental Conditions

The scotoma borders were plotted for each patient on a tangent screen and by microperimetry using a scanning laser ophthalmoscope (Rodenstock, Munich, Germany). The vertical size of the scotoma was measured along the right vertical line, taking into account the scotoma area overlying the line (Fig. 3).

We used a series of 11 figures showing two black isometric parallel vertical lines on a white background. Viewed from a distance of 30 cm, vertical lines subtended 20° of visual angle. The lines were symmetrically located at a distance of 3° on either side of the fixation point. The position of the fixation point differed in each figure, varying by 2° steps, so that altogether 11 figures with different fixation locations were presented. When the patient was fixating, the scotoma partly masked the right line. Cards, each showing a different figure, were held secure in a stand and the subject’s head was stabilized at a distance of 30 cm.

Testing Procedure

Figures were shown in random order. Patients were asked to indicate by pen on the left line the levels corresponding to the perceived upper and lower ends of the right
FIG. 3. The parallel line test. A. The three figures shown to the patients. The specific location of the fixation point is indicated by an X character on each test sheet. B. The gray Xs show the location of various fixation points on different parallel line test cards. The bold X is the actual fixation point for this particular test sheet. C. Schematic representation of perceptual shortening of the right (R) line (upper and lower arrows), corresponding to the test sheet shown in Figure 3B (patient NG). The right line appeared uninterrupted or only slightly blurred in the scotoma area.

Entire card sets were presented 4 times to patient NG and 5 times to patient CS, providing a total of 44 and 55 values for each of the upper and lower estimates. Patients were asked to report when line shortening started to manifest and to indicate the levels of perceived line shortening when this visual phenomenon became stable. These times were recorded by the examiner.

Data Analysis

We analyzed the correlation between the right line shortening and the distance from the fixation point with SPSS software. The correlation between the right line shortening and the distance of the fixation point from the end of the line was analyzed separately for the “upper” and “lower” estimates, that is, for perceived upper and lower line shortening. This approach is justified because the scotoma occluded the line ends for each location of the fixation point differently. For each subject, the relationship between line shortening and distance from the fixation point was investigated using Spearman’s rank order correlation coefficient. Each r value was converted into a z score and the observed value of z \( z_{\text{obs}} \) was calculated for the upper and lower measurement, using the following formula:

\[
z_{\text{obs}} = \frac{z_1 - z_2}{\sqrt{N_1 - 3} \cdot \sqrt{N_2 - 3}}
\]

with \( z_1 \) and \( z_2 \) being the z scores of the line shortening for the lower and upper measurements and \( N_1 \) and \( N_2 \) the respective number of trials. A nonstatistical difference would be concluded if \( -1.96 < z_{\text{obs}} < 1.96 \).

To disentangle mechanisms responsible for line shortening, the latter was plotted in terms of eccentricity in the visual field on the one hand and in terms of distance between the upper or lower line end and the closest scotoma border on the other hand.

RESULTS

A strong positive correlation between line shortening and the distance of the fixation point from the end of the line was found for both lower and upper estimates (Spearman’s correlations: subject NG: lower, \( r = 0.797, n = 55, P < 0.0005 \); upper, \( r = 0.895, n = 55, P < 0.0005 \); subject CS: lower, \( r = 0.887, n = 44, P < 0.005 \); upper \( r = 0.915, n = 44, P < 0.0005 \)). The farther the end of the line from the fixation point, the more it was perceived as...
shortened (Fig. 4). In addition, no statistical difference in the strength of the correlation was found between the distance of the fixation point and the shortening for lower and upper measurements (subject NG: \( z_{\text{obs}} \) lower/upper = 21.846, not significant (NS); subject CS: \( z_{\text{obs}} \) lower/upper = 20.72, NS).

For identical degrees of eccentricity, the magnitude of line shortening appeared similar for the upper or lower line ends. In contrast, this was not the case when identical distances between the upper or lower line end and the closest scotoma border were considered (Fig. 4).

When asked whether the lines appeared interrupted, both patients replied that they appeared continuous, and the right line appeared slightly blurred in the area passing through the scotoma. Furthermore, line shortening appeared an average of 5 seconds after steady fixation in patient NG and an average of 10 seconds in patient CS. Values of perceived line shortening were variable during the subsequent seconds, and this perceptual phenomenon became stable 15 seconds after steady fixation (for each card presentation) for patient NG and 20 seconds after steady fixation for patient CS.

The values of perceptual shortening (y coordinates) for patients NG and CS are plotted for lower and upper segments of the right line in terms of eccentricity in the visual field (x coordinates: red fonts) on the one hand and
distance from the scotoma border on the other hand (x coordinates: blue fonts).

In Figure 4, note that the further the end of the line is from the fixation point, the more it is perceived to be shortened. Moreover, for identical degrees of eccentricity, the magnitude of line shortening was similar for the upper and lower line ends. In contrast, this was not the case when identical distances between the upper or lower line end and the closest scotoma border were considered.

On the shaded areas of the graphs, the line shortening probably results from the actual masking of the line end by the scotoma. Lower line segments have larger shaded areas than the upper line segments, as the scotoma occludes the lower and upper ends of the right line differently. Specifically, the inferior end of the right line is not visible by patient NG for the successive fixation positions 0, 2, and 4 and by patient CS for the fixation positions 0 and 2. For both patients, the upper end of the right line is occluded by the scotoma when fixating at the highest fixation position.

**DISCUSSION**

In this study, we used the model of homonymous paracentral scotomas to investigate alterations in visual perception after an occipital lesion. We analyzed spatial distortion and filling-in phenomena and considered possible neural mechanisms involved in the generation of these perceptual alterations.

**Perceptual Spatial Distortion**

The right line, partly masked by the scotoma, was perceived as shorter than the left line. Perceptual line shortening varied in magnitude, depending on the location of the fixation point along the midline. Moreover, the farther the end of the line from the fixation point, the more it was perceived to be shortened.

Two factors may be involved in the variations of this perceptual phenomenon. The amount of line shortening could be related either to eccentricity in the visual field or to the effect of the scotoma overlap on the right line. Interestingly, for a given patient and eccentricity, the amount of perceptual shortening appeared similar for the lower and upper line ends, even though the scotoma occluded the lower and upper ends differently. This finding makes us believe that although the occurrence of perceptual line shortening results from scotoma overlap of the right line, eccentricity in the visual field is the predominant factor in determining the amount of this perceptual illusion. Considering that both filling-in and spatial distortion phenomena have been interpreted as an expression of cortical plasticity and that plasticity in the visual system is related to changes in the receptive fields (20), larger receptive fields in the periphery of the visual map could explain why perceptual shortening is more pronounced with increased eccentricity.

Different neural mechanisms could be involved in such perceptual alterations. It has been postulated that neurons preferentially shift their connections to the nondeprived areas of the visual field (8). It is conceivable that illusory line shortening is related to receptive field (RF) changes induced by the scotoma. RF expansion was originally observed by Gilbert and Wiesel (9) in cats with focal binocular retinal lesions. These authors noted an immediate increase in RF size for some deafferented cortical cells with receptive fields near the edge of the projected retinal scotoma. After a few months, cortical areas, which were initially silenced by the lesion, recovered visual activity. Therefore, some of the deprived cortical neurons started to become reactivated and acquired new RFs, suggesting that subthreshold inputs reached threshold at formerly unresponsive synapses. This result indicates that long-term mechanisms can induce plasticity changes in initially silenced neurons, probably through long-range horizontal connections (10).

Long-range horizontal connections between pyramidal cells in the visual cortex allow integration of information over cortical distances that are much larger than the classic model of the RF expansion and may serve as a relay for contextual information between local subsets of cells (10,11). For the RFs in the scotoma to shift, the horizontal connections must be strengthened. They do this by sprouting axon collaterals and by synaptogenesis, whereby clusters within the existing framework of horizontal connections are reinforced by adding collaterals and synaptic buttons (12). Various molecular, cellular, and physiological mechanisms play a role in visual “rewiring” and plasticity of cortical networks (13).

Whereas changes in cortical RFs have initially been described in retinal lesions, more recent studies (14,15) have shown similar changes in RFs of cortical neurons after cortical lesions. Production of focal visual cortex lesions in adult cats (14,15) has yielded an increase in the spatial extent of the RF of neurons located at the border of the lesion after a training procedure. It is therefore reasonable to postulate that RF expansion could be involved in perceptual spatial distortion reported by our patients.

Larger changes in RF size could also be related to feedback or feedforward projections from other brain structures to the visual cortex. Indeed, neurons in deep areas of V1 project intracortically, as well as subcortically, to several structures such as the pulvinar and the lateral geniculate nucleus of the thalamus (LGN), superior colliculus, and claustrum (16). Thus, neurons in these brain areas receive signals from the reorganized V1 region but interpret them according to the original retinotopic map.
as if the signals originated from visual input within the scotoma. Such mislocalization of visual signals might cause perceptual filling-in as well as distortion of visual space.

Perceptual Filling-in
Patients reported that the right line appeared uninterrupted or only slightly blurred in the scotoma area. The line completion can be attributed to perceptual interpolation that allowed visual stimuli to be perceived where there was actually no visual input (17). Similar results are obtained by the use of Amsler grids in patients with central scotomas due to macular disorders. In these patients, the area of alteration in the grid pattern is much smaller than the surface of the scotoma delineated by perimetry (18). We did not develop this specific point further, as we already had done so in earlier studies (6,18,19).

Time Course
Line shortening appeared 5–10 seconds after steady fixation was started but evolved during the following 10 seconds. These observations are in accord with our previous findings in patients with homonymous paracentral scotomas (6). Specifically, in one of our previous studies (6), in which patient NG was also tested, filling-in of the scotoma appeared 5–10 seconds after initiation of steady fixation. In the current experiment, the perceptual filling-in phenomenon was not specifically investigated, because during the testing procedure the patient was not able to pay attention and describe simultaneously two distinct perceptual phenomena. As a result, in the single patient in whom the two phenomena were investigated, a similar delay was observed in both perceptual filling-in and spatial distortion. Additional investigations using discrete stimuli (points rather than lines) could determine to what extent the two phenomena are linked.

As noted above, changes in visual afferents result in cortical reorganization, inducing perceptual alterations such as filling-in and spatial distortion. Filling-in has been widely studied and two different types, instantaneous and delayed, have been proposed, occurring after prolonged fixation (20). Rapid appearance of these phenomena can be attributed to structural changes after long-standing scotomas, whereas delayed distortion essentially happens as a result of functional and synaptic adaptation. Similar delays in the occurrence of perceptual visual alterations have been described in patients with cerebral metamorphopsia. Progressive distortion of images shown to these patients takes place a few seconds after steady fixation. Mechanisms implied in these phenomena are probably responsible for the delay of spatial distortion found in this study.

In this study, we have presented a simple way to quantify spatial distortion in the visual field after cortical lesions. Our observations show that perceptual spatial distortion extends up to 20° from the border of the scotoma and is more pronounced as eccentricity from the scotoma border increases. These observations probably reflect “long-range” cortical reorganization after brain damage. Additional investigations could broaden our understanding of mechanisms involved in this perceptual visual alteration.

REFERENCES
Abstract: Autoimmune-related retinopathy and optic neuropathy (ARRON) syndrome is characterized by visual loss and often the presence of antibodies against retinal or optic nerve antigens in the absence of cancer. Limited success has been reported in treatment of ARRON syndrome with medications that suppress the immune system. In many patients, current strategies are insufficient to control the disease. A 47-year-old woman with progressive visual and hearing loss attributed to ARRON syndrome that was resistant to conventional therapies underwent autologous hematopoietic stem cell transplantation (HSCT). Clinical manifestations appeared to stabilize. This report suggests that autologous HSCT may have a therapeutic role in ARRON syndrome.

Several treatments based on standard therapy for autoimmune disorders have been tried in ARRON syndrome with variable success, including prednisone, intravenous methylprednisolone (IVMP), immunosuppressive agents, plasma exchange, and intravenous immunoglobulin (IVIg) (1,9–16). We describe what we believe to be the first reported patient to be treated with autologous HSCT.

CASE REPORT
In February 2001, a 47-year-old Caucasian woman presented for evaluation of visual loss. Her vision had deteriorated over the preceding 7 months with complaints of worsening glare from fluorescent lights, blurred vision in both eyes, and impaired night and color vision. She did not report photopsias. Her visual loss coincided with the onset of bilateral progressive hearing loss and episodes of high-pitched tinnitus. In addition, she described the sensation of “pins and needles” in her feet that over the next several months had evolved into bilateral lower extremity numbness and paresthesias. Over a 6-year follow-up, the patient developed bladder incontinence, disturbance in balance, and Sjögren syndrome (17).

In 1992, she had had Mycoplasma pneumonia and shortly thereafter chronic fatigue, polyarticular arthritis, and hypothyroidism with a thyroid biopsy yielding a benign nodule.

Family history included a malignant melanoma in an identical triplet sister, her brother, and a cousin. Neither of her triplet siblings had connective tissue disease.

In March 2001, our evaluation showed a visual acuity of 20/30-1 in the right eye and 20/25-1 in the left eye. Color vision tested on the American Optical Hardy-Rand-Rittler (AOHRR) plates was 2/6 in the right eye and 1/6 in the left eye (Note that the patient eventually lost color vision: 0/6 in both eyes on the AOHRR plates). Pupils were of normal size and reactivity without afferent defect. There was no evidence of inflammation in the eye.
Ophthalmoscopy demonstrated moderate optic disc pallor with attenuated blood vessels bilaterally.

Humphrey (stimulus size III) visual field examination showed further deterioration compared with an examination performed 1 month earlier. The mean deviation in the right eye had decreased from 9.1 to 13.38 dB with overall depression; the mean deviation in the left eye had decreased from 11.44 to 14.72 dB with a superior altitudinal defect.

Neuro-otologic examination demonstrated bilateral vestibular dysfunction with disruption of the vestibulo-ocular reflex and bilateral sensorineural hearing loss that proved to be progressive over the course of follow-up.

On neurologic examination, the patient exhibited decreased vibratory sensation in the toes and could not perform a tandem gait. Quantitative sensory studies and nerve biopsy, showing axonal and demyelinating changes, were consistent with a sensorimotor peripheral neuropathy. Brain MRI in January 2001 did not reveal any evidence of a demyelinating disease.

Additional studies with normal results included complete screening for heavy metals, human immunodeficiency virus, hepatitis, paraneoplastic disorders, serum homocysteine, and Lyme titer; immune electrophoresis; and SS-A/Ro, SS-B/La, rheumatoid factor (RF), antinuclear antibodies (ANA), antimicrosomal antibodies (AMA), anti-neutrophil cytoplasmatic antibodies (ANCA), double-stranded DNA, anti-smooth muscle antibody (ASMA), fluorescent treponemal antibody absorption test (FTA-ABS), VDRL test, rapid plasma reagin (RPR) and microhemagglutination Treponema pallidum (MHA-TP), and vitamin B$_{12}$. Hematologic testing demonstrated macrocytosis.

Results of lumbar puncture, colonoscopy, chest CT, mammogram, dermatologic skin survey, and bone marrow biopsy were negative. On Western blotting, the patient’s serum did not demonstrate any cancer-related retinal proteins. In the absence of malignancy, the patient’s condition was considered most consistent with ARRON syndrome.

In April 2001, the patient began treatment with 20 mg prednisone three times daily (Fig. 1).

The patient’s serum collected in December 2001 was evaluated for antibody activity against pig retina (Table 1A) and optic nerve (Table 1B). Specific regions of reactivity on the Western blot, designated by their respective molecular masses, were compared with the relative incidence of antibody activity of serum from 100 normal postmenopausal women volunteers as control serum. Table 1A reports the findings when the patient’s sera and the sera of the normal control population were reacted against pig retina. Table 1B reports the results of reactions against pig optic nerve.

Despite prednisone treatment and other immunologic treatments outlined in Fig 1, the patient gradually lost vision. Optic disc pallor became profound. By March 2002, Humphrey visual fields could no longer be obtained, and Goldmann perimetry showed generalized constriction.

In September 2003, the patient was found to have very low counts of lymphocyte subsets compared with a normal lymphocyte phenotype done in 2001. Serologic testing for anti-heat shock protein (hsp)-70, associated with autoimmune inner ear disease, showed positive results. Antiphospholipid antibody (APA) IgM was elevated (14.9), consistent with a generalized autoimmune disorder.

In January 2004, the patient was referred to Northwestern University for evaluation of an autologous nonmyeloablative HSCT protocol approved by the institutional review board and Food and Drug Administration Investigational New Drug (IND) 11669. Hematopoietic stem cells (HSCs) were harvested. The immune ablative regimen was 200 mg/kg intravenous cyclophosphamide and 20 mg CAMPATH-IH.

In September 2004, unmanipulated autologous stem cells were infused. White blood cell and platelet counts recovered on day 10.

In March 2005, she reported increased energy, improved gait, vision, and hearing, as well as decreased spasms of the lower extremities and complete resolution of bladder dysfunction. Her chief complaints were extremity pain and photophobia and foreign body sensation in the eyes attributed to dryness.

In June 2005, audiometric testing showed a 5–10 dB improvement in pure tone threshold and a 10–15 dB improvement in speech reception threshold. Subsequent studies have demonstrated the patient’s hearing to be stable.

In April 2006, serum was collected again and reevaluated for antibody activity against pig retina (Table 1A) and optic nerve (Table 1B). After HSCT, there was a reduction in the total number of antibodies against both target tissues. But there was also some new antibody activity. The significance of these changes is unknown.

In August 2006, ganzfeld electroretinography (ERG) and multifocal electroretinography (mERG) showed slight improvement relative to results from July 2004. The pretransplant photopic B wave measured at 67.1 mVs right eye and 66.5 mVs left eye had improved to 75.4 mVs right eye and 88.9 mVs left eye (normal: 75.9–175.9 mVs). Similarly, the photopic flicker had improved from 62.0 mVs right eye and 57.1 mVs left eye to 72.0 mVs right eye and 77.8 mVs left eye (normal: 62.3–212.1 mVs). The scotopic B wave had improved from 400.6 mVs right eye and 376.5 mVs left eye to 458.5 mVs right eye and 468.9 mVs left eye (normal: 353.9–752.1 mVs). Although the right eye mERG revealed no difference after treatment, the left eye mERG demonstrated resolution of three of four points that were beyond 2 SDs from normal in the paracentral region.

In October 2006, visual acuity was 20/40 in both eyes with appreciation of the fly, 3/3 animals, and 5/9 circles
FIG. 1. Time course of patient’s treatments and visual functional outcomes. Note that worsening of visual function occurred when the patient had discontinued intravenous immunoglobulin (IVIg) therapy and that improvement occurred after hematopoietic stem cell transplantation (HSCT). Key to treatment epochs: 1, April 2001: start 20 mg prednisone three times daily; May 2001: add methotrexate; June 2001: discontinue prednisone and methotrexate and start plasma exchange followed by IVIg and cyclophosphamide. 2, December 2001: start plasmapheresis followed by 0.4 g/kg IVIg monthly; August 2003: discontinue IVIg. Note acute worsening of visual acuity. 3, January 2004: resume monthly 0.4 g/kg IVIg; September 2004: perform HSCT.
TABLE 1. Our patient’s antibody reactions against pig retina and optic nerve

<table>
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<tr>
<th>Antibody Activity Before HSCT, 12/12/01 (kDa)*</th>
<th>Relative Incidence of Antibody Activity in Control Group</th>
<th>Antibody Activity After HSCT, 4/26/06 (kDa)*</th>
<th>Relative Incidence of Antibody Activity in Control Group</th>
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*HSCT, hematopoietic stem cell transplant. NA, not available.

DISCUSSION

Because of the paucity of cases of ARRON syndrome, there is no reliable information on whether treatment is effective (1,9–16,18–32). The general approach consists of treating the underlying systemic disease if one is present. In the absence of a systemic disease, corticosteroids have been used first. Depending on the response to corticosteroid treatment, cyclophosphamide, methotrexate, IVlg, and plasmapheresis have been used singly or in combination.

In our patient, progressive hearing and visual loss was slowed by IVlg treatment (Fig. 1), whereas the peripheral symptoms continued to worsen. The non-myeloablative HSCT regimen used to treat this patient was selected because an identical regimen has been used safely and with promising results in systemic lupus erythematosus, other autoimmune diseases, and type I diabetes mellitus (33–37). In our patient, HSCT was well tolerated; there was an improvement in symptoms and a reversal of declining visual fields and acuity. There was also a reduction in the total number of antibodies after HSCT against both retina and optic nerve, but some new antibody activity was demonstrated. The significance of these phenomena is unknown.

The nosology of ARRON syndrome remains controversial. The first reports (18–23) of autoimmune optic neuropathy described patients with corticosteroid-responsive optic neuropathy, who had an idiopathic acute or subacute asymmetric loss of vision that improved after immunomodulation treatment. The available techniques did not allow detection of antibodies against retina and optic nerve. ERGs were not routinely used to evaluate retinal function. Later, patients with this condition were found to have antibodies to various layers of the retina and optic nerve (3,24–26). ERG abnormalities were frequently described and antibodies against recoverin (23 kDa) (24), Müller cells (25), a 22-kDa antigen (26), a 35-kDa antigen, and a 46-kDa antigen were eventually reported (6).

In 2004, the term autoimmune retinopathy (AR) was applied to patients who presented with paraneoplastic-like retinopathy in the absence of malignancy (6). All patients had ERG changes and nearly half had autoantibodies against retinal antigens. Other studies in patients with optic nerve dysfunction began to show a variety of autoimmune reactions to optic nerve and retina (1,7,26).
patients who did not show antibodies to retina or optic nerve, the absence of these antibodies has been attributed to impaired detection, individual sampling variation, or the immunosuppressed state of the patient undergoing treatment. The investigational challenge is further increased in the absence of a standardized control and method of study. To date, there are too few publications describing the prevalence of these antibodies in a large normal control group (27,38).

We agree with Shimazaki et al (27) that because anti-retinal antibodies are present in a majority of normal control human sera, newly detected retinal autoantigens should be interpreted with caution and subject to rigorous testing for disease association. For this reason, we used 100 normal women as control subjects for our retina and optic nerve antibody determinations. Despite these normal control subjects, however, we do not know if the changes seen in our patient’s serum represent more than an epiphenomenon (28).

We favor the term ARRON syndrome because it encompasses a disease spectrum that includes cases of retinal involvement, optic nerve involvement, and simultaneous retinal and optic nerve involvement. Table 2 is our attempt to define ARRON syndrome.

ARRON syndrome appears to be more common in women than men (2:1), with an average age of 50 years (range 37–75 years) (1,6). The visual loss is often asymmetric, with visual acuity varying from 20/20 to no light perception. ERG abnormalities are present in the majority of patients. In one report in which ophthalmoscopic findings were reported, 11 of 12 patients had optic disc pallor (1). In that report, nonspecific retinal changes were present in 8 of 12 patients (1). In the 58 patients for whom fundus findings were not reported, ERG abnormalities were found in all (6). In reports in which other clinical information is provided, 8 of 12 patients had other systemic autoimmune diseases (1).

The pathophysiology of autoimmune retinal and optic nerve degeneration in ARRON syndrome remains uncertain. Studies have demonstrated the specificity of anti-recoverin antibody, which stains photoreceptors, and
TABLE 2. Suggested diagnostic criteria for autoimmune-related retinopathy and optic neuropathy (ARRON) syndrome

All four of the following:
1. Visual loss as demonstrated either by visual acuity or visual field examination
2. No malignancy found after extensive evaluation*
3. Evidence of optic nerve or retinal abnormalities
4. No identifiable cause for optic neuropathy and/or retinopathy

One of the following:
1. Serum autoantibodies against retina and/or optic nerve not usually found in normal healthy individuals†
2. Response to immunomodulation demonstrated either by stabilization, slowing, or reversal of visual deficit

Modifiers:
Type A: Associated with other autoimmune disease
Type B: Not associated with other autoimmune disease

*Includes a history of remote malignancy that may better explain visual loss as being associated with cancer-associated retinopathy (CAR), paraneoplastic optic neuropathy (PON), and melanoma-associated retinopathy (MAR).†The presence of autoantibodies to retina and/or optic nerve antigens does not prove causality.

anti-47-kDa antibodies, which stain ganglion cells, bipolar cells, and Müller cells (25,26,30). Other reports showed sera to have nonspecific retinal staining and optic nerve staining (1). Anti-hsp-70, anti-enolase, and anti-recoverin sera to have nonspecific retinal staining and optic nerve cells, and Müller cells (25,26,30). Other reports showed retinal elements, specifically S-antigen and recoverin, in-duce ERG changes in animal models (40). Adamus et al (5) have demonstrated that anti-recoverin antibodies induce an increase in intracellular calcium, leading to retinal cell death via a mitochondrial apoptotic pathway. In addition, nifedipine has been found to protect against anti-recoverin-induced apoptosis. (5) These studies imply a direct and specific role for autoantibodies in loss of visual function.

An extensive evaluation to rule out malignancy must be undertaken before the diagnosis of ARRON can be assigned. Patients with cancer-associated retinopathy (CAR), paraneoplastic optic neuropathy (PON), or melanoma-associated retinopathy (MAR) will often initially manifest visual dysfunction and only later be found to have a malignancy (29,45). Our recommendation for screening includes whole body imaging, bone marrow biopsy, dermatologic skin survey, colonoscopy, standard prostate screening, gynecologic examination, mammography, lumbar puncture, and serum testing for recoverin (29,45) and the 62-kDa neuronal antigen called collapsin response-mediating protein-5 (CRMP-5) (29,45,46).

REFERENCES
Optic Neuropathy Caused by Naso-Orbital Mass in Chronic Intranasal Cocaine Abuse

Christopher C. Shen, MD, Amanda L. Silver, MD, Thomas J. O’Donnell, MD, James C. Fleming, MD, and Zeynel A. Karcioglu, MD

We describe a patient in whom chronic intranasal cocaine use produced a bone-destructive, fibro-inflammatory, naso-orbital lesion that damaged the optic nerve and masqueraded histopathologically as a soft tissue neoplasm. The histopathologic findings of cocaine abuse may mimic either a neoplasm or necrotizing vasculitis and could prove especially confusing if a history of cocaine abuse is not known.

CASE REPORT

A 48-year-old African-American woman presented to the emergency room with a history of slowly progressive proptosis and loss of vision in her right eye with intermittent epistaxis over the previous year. She had had uterine fibromyomas and anemia. She admitted to chronic intranasal cocaine abuse and heavy cigarette smoking.

Visual acuity was count fingers at 1 foot in the right eye and 20/30 in the left eye, with a right afferent pupillary defect. Applanation intraocular pressures were normal. She had 5 mm of right axial proptosis. Extraocular movements were limited in the right eye in all directions. The conjunctiva of the right eye was chemotic and hyperemic. Ophthalmoscopy disclosed marked optic disc pallor in the right eye.

Head CT revealed an absent nasal septum accompanied by bony erosion of the ethmoid, sphenoid, and maxillary sinuses and nasolacrimal drainage system. Optic neuropathy, proptosis, ophthalmoplegia, corneal lesions, and transient monocular blindness have also been reported.

Abstract: A 48-year-old woman with a history of chronic intranasal cocaine abuse presented with unilateral proptosis associated with severe visual loss from optic neuropathy in the right eye. Imaging showed extensive bone and soft tissue destruction in the paranasal region and an orbital mass. Initial biopsies suggested a low-grade neoplasm. The correct diagnosis was established only on repeat biopsy, which revealed marked pleomorphism and non-specific chronic inflammation with irregular collagen bundles containing thick-walled blood vessels. This case emphasizes that intranasal cocaine abuse may clinically, radiographically, and histopathologically mimic a neoplasm or a necrotizing vasculitis.

Cocaine is a naturally occurring alkaloid of the coca plant Erythroxylon coca. Its pharmacologic effects are due to stimulation of the central and sympathetic nervous systems and augmentation of the normal effects of the neurotransmitter norepinephrine. It produces anesthesia by inhibiting excitation of nerve endings or by blocking conduction in peripheral nerves by reversibly binding to and inactivating sodium channels.

Chronic intranasal cocaine abuse is known to cause local vasoconstriction and ischemic necrotizing inflammation of soft tissues, cartilage, and bones of the paranasal sinuses and nasolacrimal drainage system. Optic neuropathy, proptosis, ophthalmoplegia, corneal lesions, and transient monocular blindness have also been reported.

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FIG. 1. Axial (A), coronal (B), and sagittal (C) CT performed at presentation show forward and lateral displacement of the right eye and a large nasosinusoidal defect communicating with the right orbit (arrows). A poorly delineated inflammatory mass is best seen on the coronal and sagittal views (asterisk).

reveal any causative organisms. Nasal cultures revealed multiple organisms, including Proteus mirabilis, Staphylococcus aureus, and group A -streptococcus. She received a course of intravenous vancomycin and ceftriaxone.

Because of worsening proptosis, she underwent an inferior orbitotomy and orbital incisional biopsy 2 months later. This sample disclosed necrotizing inflammation and extensive fibrosis. Because of the active nature of the fibrous proliferation, a low-grade fibrous tumor could not be excluded.

Because of persistent proptosis, she underwent an orbital decompression procedure 7 weeks later. Tissue samples from this third procedure showed nonspecific chronic inflammation and active fibrosis. Diffuse, irregular collagen bundles containing thick-walled blood vessels with focal chronic inflammatory cell deposits were present. In some areas fibroblastic proliferation was exuberant. Although there was marked pleomorphism, no mitotic figures were seen (Fig. 3). No amyloid was detected with Congo red stain. Pathologists were now satisfied that this was not a neoplasm or a primary vasculitis.

DISCUSSION

This case illustrates that chronic cocaine abuse may produce confusing histopathologic abnormalities and that several biopsies may be needed to clarify the diagnosis.

In otorhinolaryngologic and oculoplastic procedures, cocaine may be used topically in very short duration for its vasoconstrictive and local anesthetic properties without untoward consequences (7). When cocaine is used chronically, however, these actions become detrimental. Vasoconstriction induces mucosal and submucosal tissue ischemia and leads to varying degrees of destruction of soft and bony tissues (8–11). With long-standing intranasal use, cocaine causes progressive destruction of the mid-facial structures, including the hard and soft palate, nasal septum, nasal turbinates, nasal ala, ethmoid sinuses, and adjacent tissues. Patients may ultimately develop nasal collapse, including saddle-nose deformity and oronasal fistula (8–13). The pathophysiology of intranasal tissue loss includes secondary infection, impaired mucociliary transport, decreased humoral and cell-mediated immunity, and chemical irritation from adulterants put into “cut” cocaine (3,14).

Optic neuropathy in chronic cocaine abusers is thought to be due to ischemic necrosis of the soft tissues in close proximity to the optic nerves (2). The sphenoid sinus is directly medial to the optic canal and in approximately 5% of individuals, the bony wall separating these structures may be incomplete, putting these patients at high risk of complications (15).

The differential diagnosis for intranasal destructive processes includes inflammatory, neoplastic, infectious, and idiopathic etiologies (Table 1) (16–21). The term “lethal midline granuloma,” formerly used to encompass a range of conditions including Wegener granulomatosis, lymphoma, carcinoma, tuberculosis, and invasive fungal infection, is now considered outdated. A specific diagnosis should be made based on clinical and morphologic characteristics as well as diagnostic studies (22).
FIG. 2. Histopathology from the first biopsy shows necrotic nasal epithelium and an underlying subepithelial inflammatory reaction composed of polymorphonuclear cells, eosinophils, lymphocytes, and plasma cells at different magnifications. (Hematoxylin and eosin.)

FIG. 3. Histopathology from the third orbital procedure shows diffuse irregular collagen deposits with focal chronic inflammatory cells. Entrapped thick-walled blood vessels (white arrows) indicate the long-standing nature of the inflammation. The high-power magnification (lower image) shows proliferating fibroblasts (black arrows). Although there was marked cellular pleomorphism, no mitotic figures were seen. (Hematoxylin and eosin.)

Clinical suspicion and a thorough history and physical examination are critical for accurate diagnosis. Laboratory workup can include ESR, renal function, ANA, RPR, nasal cultures, angiotensin-converting enzyme (ACE) level, and c-ANCA. Urine and serum toxicology studies may be helpful in cases of suspected cocaine abuse. Neuroimaging may facilitate demarcation of the extent of the nasal disease but may not be helpful in distinguishing between potential etiologies. For patients with significant sinonasal ulceration and necrosis, a biopsy should be performed. With intranasal cocaine use, biopsy of the affected tissue for histopathologic studies may reveal focal areas of chronic inflammation and necrosis, but typically will not show the necrotizing granulomas or vasculitis typical of Wegener granulomatosis (17). Flow cytometry
reflect the repetitive nature of the chemical insult by the thickened. The presence of thick-walled vessels in other areas, the walls of similar-diameter vessels were not walled capillaries were present within fibrous areas, but in atypia or mitotic figures were seen. In some areas, thick-

and T-cell gene rearrangement studies may be helpful in ruling out lymphoma. Persistent investigation is often necessary to confirm a diagnosis in these difficult cases. Frequent biopsies and repeat laboratory studies may be necessary, especially because the diagnosis of Wegener granulomatosis can be difficult to make if the disease is confined to the sinonasal cavity (23,24).

In our patient, histopathologic findings consisted of a wide range of inflammation, from necrotizing acute changes to chronic inflammation in a perivascular distribution with scattered dense fibrosis. The alternating areas of acute and chronic inflammation and focal dense fibrosis reflect the repetitive nature of the chemical insult by the cocaine abuse. As certain parts of the tissue attempt to heal with fibrosis, other areas become involved with newly developing acute ischemia and necrosis. This pattern of inflammation probably stimulates fibroblastic proliferation to produce irregular dense collagen fibers and atypical-appearing fibroblasts (Fig. 3). Such a pattern, seen most prominently in the second biopsy of our patient, raised the question of a low-grade fibrous tumor. Alexandrakis et al (5) reported a similar finding in their Case 1. In our patient, many pleomorphic fibroblasts were present, but no tumor atypia or mitotic figures were seen. In some areas, thick-walled capillaries were present within fibrous areas, but in other areas, the walls of similar-diameter vessels were not thickened. The presence of thick-walled vessels in fibroproliferative tissue is another indication of a long-standing inflammatory process affecting different regions of the tissue at different times.

**TABLE 1. Differential diagnosis of necrotizing sino-orbital inflammation**

| Inflammatory ("granulomatous") diseases |
| Wegener granulomatosis |
| Sarcoidosis |
| Relapsing polychondritis |
| Systemic lupus erythematosus |
| Mixed connective tissue disease |
| Neoplastic diseases |
| Nasal angiocentric lymphoma (polymorphic reticulosis) |
| Non-Hodgkin lymphoma including nasal-type natural killer/T-cell lymphoma (NK/T-cell lymphoma) |
| Infectious diseases |
| Recurrent bacterial sinus infections |
| Syphilis |
| Fungal infections of the orbit and paranasal sinuses including Fusarium and Mucormycosis |
| Idiopathic disorders |
| Idiopathic midline destructive disease |
| Orbito-sino-nasal allergic fungal inflammation |

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**REFERENCES**

Stereotactic Radiosurgery in Two Cases of Presumed Fourth Cranial Nerve Schwannoma

Evis Petrela, MD, Charles J. Hodge, MD, Seung S. Hahn, MD, Chung T. Chung, MD, and Luis J. Mejico, MD

Abstract: A 47-year-old woman and a 45-year-old man with gradually progressive fourth cranial nerve palsy underwent stereotactic radiosurgery for presumed fourth cranial nerve schwannomas with the gamma knife at a marginal tumor dose of 14 and 13 Gy, respectively. In one patient, the ocular misalignment disappeared; in the other patient, it stabilized. MRI showed shrinkage of the tumors. These patients represent the second and third reported cases of presumed fourth cranial nerve schwannoma treated with radiosurgery and the first cases with substantial follow-up information.

Intracranial schwannomas have been reported to occur in association with neurofibromatosis and less commonly without this condition (1–3). Usually they arise from sensory nerves but they have also been reported in a number of mixed and purely motor cranial nerves. Fourth cranial nerve schwannomas may present clinically by causing dysfunction of the nerve from which they arise by causing dysfunction of neighboring structures (1–3). Clinical and radiological observation has been suggested for small isolated fourth cranial nerve schwannomas measuring less than 5 mm in size (1), whereas surgical intervention is recommended for larger lesions with mass effect on neighboring structures (2–5).

We report the clinical outcome at 2 years of patients with gradually progressive fourth cranial nerve palsy caused by presumed schwannomas arising within that nerve and treated with stereotactic radiosurgery.

CASE REPORTS

Case 1

A 47-year-old woman presented with new binocular diplopia of 6 weeks’ duration. There had been no head trauma, and the patient lacked conventional risk factors for arteriosclerosis. There were no other ocular or neurologic symptoms, and there was no family history of neurofibromatosis.

The ophthalmologic examination was normal except for left hypertropia of 4 prism-diopters in primary gaze position that worsened to 6 prism-diopters on right gaze and on left head tilt. Skin examination did not reveal the stigmata of neurofibromatosis.

The baseline complete blood count, cholesterol levels, fasting glucose levels, thyroid tests, and acetylcholine receptor antibodies showed no abnormalities.

Brain MRI (Fig. 1) demonstrated a left enhancing extra-axial lesion adjacent to the midbrain just below the tentorial notch, measuring 7 mm in the largest diameter. Cerebral angiography revealed no evidence of aneurysm or vascular malformation. A presumptive diagnosis of left fourth cranial nerve palsy caused by schwannoma was made.

No intervention occurred, but at 3 months the left hypertropia in primary gaze had worsened to 6 prism-diopters and at 6 months to 10 prism-diopters, so the patient underwent stereotactic radiosurgery 6 months after the onset of symptoms. The procedure was performed using the Leksell gamma knife (Elekta Instruments, Norcross, GA). An 8-mm collimator time single shot was used to deliver a marginal tumor dose of 14 Gy to the 70% isodose line. The tumor volume was measured to be 0.168 mL.

A few months after treatment, the patient reported resolution of diplopia. She remained asymptomatic after 2 years. Examination then disclosed normal ocular alignment in all gaze positions. MRI at 2 years after treatment showed a decrease in the size of the lesion (Fig. 1).

Case 2

A 45-year-old man presented with new diplopia of 8 weeks’ duration. There had been no head trauma and the
FIG. 1. Case 1. Brain MRI performed before (A–C) and 2 years after (D–F) stereotactic radiosurgery for a presumed left fourth cranial nerve schwannoma. There is an extra-axial lesion (arrows) adjacent to the midbrain below the tentorial notch measuring 7 mm in the largest diameter. It is isointense to brain parenchyma on precontrast T1 (A) and T2 (B) images and enhances homogeneously on the postcontrast T1 (C) image. Two years after treatment, there is a decrease in the size of the lesion on corresponding MRI sequences (D–F).

The patient lacked conventional risk factors for arteriosclerosis. There were no other ocular or neurological symptoms, and there was no family history of neurofibromatosis.

Ophthalmic examination was normal except for a right hypertropia of 4 prism-diopters in primary gaze position that worsened to 18 prism-diopters in left gaze and 9 prism-diopters on right head tilt. One month earlier, the referring ophthalmologist had documented a right hypertropia of 2 prism-diopters in primary gaze. Skin examination did not reveal the stigmata of neurofibromatosis.

The baseline complete blood count, cholesterol levels, fasting glucose levels, thyroid tests, and acetylcholine receptor antibodies showed no abnormalities. Brain MRI demonstrated a 3-mm enhancing lesion in the right side of the midbrain (Fig. 2). A presumptive diagnosis of right fourth nerve palsy caused by schwannoma was made.

Initial management consisted of clinical observation, but the patient’s right hypertropia in primary gaze had increased to 6 prism-diopters at the 3-month follow-up visit and to 8 prism-diopters at the 6-month follow-up visit.
FIG. 2. Case 2. Brain MRI performed before (A–C) and 2 years after (D–F) stereotactic radiosurgery for a presumed right fourth cranial nerve schwannoma. There is an extra-axial lesion (arrows) adjacent to the midbrain measuring 3 mm in its largest diameter. It is isointense on precontrast T1 (A) and T2 (B) images and homogenously enhances on the postcontrast T1 (C) image. Two years after treatment, there is a slight decrease in the size of the lesion on corresponding MRI sequences (D–F).

Therefore, at 6 months after the onset of symptoms, the patient underwent stereotactic radiosurgery using the Leksell gamma knife. A 4-mm collimator time single shot was used to deliver a marginal tumor dose of 13 Gy at the 68% isodose line. The tumor volume was measured to be 0.039 mL. At the 2-year follow-up visit, the ocular alignment had not changed. MRI at that time showed a decrease in the size of the lesion (Fig. 2).

**DISCUSSION**

Our two patients presented with worsening binocular diplopia and their ocular alignment measurements were consistent with gradually progressive fourth cranial nerve palsy. In each case, MRI demonstrated an enhancing lesion along the path of the fourth cranial nerve at the midbrain level.

Common intrinsic lesions of the fourth cranial nerve include schwannomas, neurofibromas, neurilemomas, hemangiomas, and their malignant counterparts (1,6). Rarely CSF spread of metastatic disease and lymphomas can appear as focal cranial nerve masses (7). The ultimate diagnosis of a tumor in this location requires histologic evaluation, but biopsy is likely to cause permanent dysfunction of the nerve. Improvement in neuroimaging techniques has offered advantage in the diagnosis of these tumors. Mulkens et al (8) reviewed the MRI characteristics of 84 acoustic schwannomas, including 52 with pathologic diagnosis, and found that precontrast isointensity of the lesion to brain parenchyma and postcontrast intense homogeneous enhancement were characteristic of schwannoma.

Cranial nerve schwannomas occur rarely in the absence of neurofibromatosis, as was the case in our two patients. Accounting for approximately 8% of intracranial neoplasms (1), they most commonly arise from sensory (vestibular and trigeminal) nerves. (6). Schwannomas of motor nerves and, more specifically of the fourth cranial nerve, are extremely rare. There are only 36 reported cases (4), 27 confirmed by biopsy (2). Their natural course is therefore not well known. Left untreated, they usually enlarge gradually (3) and may rarely undergo intrinsic bleeding that causes rapid worsening of symptoms (4). On occasion, they may remain stationary (1). Feinberg et al (1)
reported 6 cases of schwannomas that measured less than 5 mm in greatest diameter in patients who were followed over a period ranging from 11 to 26 months. Five tumors did not demonstrate progression, either clinically or radiologically. These authors suggested that initial observation with serial imaging is the appropriate management for small, isolated presumed schwannomas of the fourth cranial nerve that remain clinically stable.

Surgical resection via retrosigmoid (2), subtemporal, and lateral suboccipital (3) approaches has been undertaken when fourth cranial nerve schwannomas measure between 10 and 45 mm in largest diameter and exert mass effect on neighboring tissues causing neurologic deficits such as hemiparesis, cerebellar ataxia, sensory disturbance, headaches, dysarthria, or vertigo. Unfortunately, morbidity associated with surgical resection can be substantial. All patients who underwent surgery developed permanent complete fourth cranial nerve palsy postoperatively, leading Ture et al. (3) to conclude that it is very difficult to remove these tumors without compromising function. Thus, in our two patients with small tumors who had gradual worsening of their diplopia and strabismus over a 6-month observation period, surgical excision was not a good option given the lack of associated neurologic symptoms and the high reported morbidity. Therefore, the decision was made to treat both with stereotactic radiosurgery.

Patients with intracranial schwannomas respond particularly well to stereotactic radiosurgery owing to the noninfiltrative nature of the tumor and the relatively high resistance of most cranial nerves to radiation toxicity (9–11). Stereotactic radiosurgery is preferred over fractionated therapy because of its convenience (treatment is completed in 1 day) and the fact that it provides precise delivery of radiation to small targets with rapid dose fall-off so as to spare adjacent structures (12).

Stereotactic radiosurgery has been performed successfully in patients with small to moderate size vestibular (10) and nonvestibular schwannomas without symptomatic mass effect (5) to minimize surgical excision-related morbidity of such benign tumors. Most of the data come from treatment of these relatively common tumors, for which stereotactic radiosurgery offers a high control rate but continues to pose a risk for cranial nerve damage. In a recently published series, Chopra et al (11) reported 98.3% tumor control rate at the 5- to 10-year-follow-up in 216 vestibular schwannomas treated with marginal tumor doses of 12–13 Gy. However, these authors found that progressive hearing loss may continue in the long term. Pollock et al (5) reported 23 patients with small to medium size nonvestibular schwannomas treated with stereotactic radiosurgery and concluded that this treatment offers less morbidity and very low tumor recurrence rate. In their series they included only one patient with a fourth cranial nerve schwannoma and provided no information about clinical outcome for that patient.

In our patients, previous radiation dose regimens shown to be safe and effective for treating acoustic schwannomas seemed a reasonable choice (11). Neither patient had complications from treatment. The first patient had complete resolution of symptoms and remained orthophoric at the 2-year follow-up, whereas our second patient had immediate and prolonged stabilization of diplopia at a level well controlled with prism glasses. Posttreatment MRIs demonstrated a decrease in size of the lesions in both patients and repeat MRIs at a 2-year follow-up have not demonstrated regrowth.

Our study is limited by the fact that we are reporting only two cases. Further studies and longer follow-up are necessary to demonstrate the short- and long-term efficacy of stereotactic radiosurgery as the primary treatment for small to medium size presumed fourth cranial nerve schwannomas with worsening symptomatology.

REFERENCES

Retinal Arteriolar Spasm During Transient Monocular Visual Loss in Eosinophilic Vasculitis

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Abstract: A patient with eosinophilic vasculitis and acquired immunodeficiency syndrome (AIDS) developed episodic transient monocular visual loss. During or immediately after two visual loss episodes, we demonstrated narrowed retinal arterioles, delayed arterial filling time, and segmented retinal venous flow in the affected eye on fundus photography and fluorescein angiography (FA). Such findings have only rarely been reported in patients with transient monocular visual loss in other conditions, probably because the episodes have ended before fundus photography and FA could be performed. This is the first report to capture retinal vascular changes associated with transient monocular visual loss in a patient with eosinophilic vasculitis.


A 57-year-old African-American man was referred to our service because of an 8-month history of episodic bilateral transient visual loss. During our examination, he experienced sudden, painless visual loss to light perception...
in the right eye lasting 2 minutes. Twenty minutes after the conclusion of this episode, vision returned to his baseline of 20/25, and fundus photographs were obtained. They showed segmentation in the blood columns of the retinal veins (”box-carrying”) and attenuated retinal arteries in the right eye (Fig. 1A) and no abnormalities in the left eye (Fig. 1B). Sixty minutes after the end of the amaurotic episode, blood flow in the right eye had returned to normal (Fig. 2).

A fluorescein angiogram (FA) was performed 75 minutes after the amaurotic episode had concluded. Initial frames of the FA appeared normal in both eyes. During the angiogram, the patient suffered a second amaurotic episode. Within 20 seconds after he reported right eye visual loss to the light perception level, decreased perfusion was apparent in the right eye on the FA (Fig. 3). Perfusion and vision returned to normal after 5 minutes. The perfusion of the left eye remained normal throughout the FA. Optic nerve head hyperfluorescence was evident in the late phase of the angiogram in both eyes (Fig. 3).

The patient was admitted to the hospital and treated with heparin (15 U/kg/h). He did not report any further episodes of visual loss after 24 hours of heparin therapy. Results of a FA performed after 48 hours of heparin therapy were normal. Carotid ultrasound examination showed low internal carotid artery velocities without stenosis. Findings from aortic arch, neck, and brain MRI and MRA were significant for an old left occipital lobe infarct. Results of a transesophageal echocardiogram were normal.

The patient had the diagnosis of acquired immune deficiency syndrome (AIDS) 20 years earlier. His current CD4 count and viral load were 59 cells/mm³ and 31,000 copies/ml, respectively.

Because prominent tender, pulsating temporal arteries were noted bilaterally and the erythrocyte sedimentation rate was 46 and C-reactive protein was 15 (normal 0–10), a temporal artery biopsy was performed. Histopathologic analysis of the biopsy specimen revealed eosinophilic leukocytic infiltration of the intima and media consistent with a diagnosis of eosinophilic vasculitis (Fig. 4). A review of the patient’s blood studies demonstrated persistent eosinophilia, ranging from 900 to 6,600 eosinophils/mm³ over the previous 3 months. Therapy with 80 mg/day oral prednisone was started, and the eosinophil level returned to normal (<500) within 1 week.

During the next 18 months, the patient underwent a very slow taper of prednisone and was then maintained on 1 mg/day prednisone, together with warfarin and highly active antiretroviral treatment. He was free of systemic and visual symptoms during this period and returned to work and other regular activities, which included running a few miles per day.

The vascular changes associated with transient monocular vision loss have rarely been photographed (1–4). Others have captured vasospasm associated with concurrent transient monocular vision loss photographically during exercise (1) and angiographically in retinal migraine (2) and impending central retinal vein occlusion (3). However, the
present report is the first to demonstrate such a phenomenon in an FA for a patient with eosinophilic vasculitis.

Eosinophilic vasculitis is a condition in which eosinophil levels in the blood are abnormally high. Eosinophils infiltrate tissues, including the walls of blood vessels, and cause local inflammatory damage. This condition may manifest in isolation or in association with systemic vasculitides such as Churg-Strauss syndrome, connective tissue diseases, malignancies, drug hypersensitivities, and infections, including AIDS, as in our patient (5–10).

Schwartz et al (11) reported a case similar to the present one in which a patient with eosinophilic vasculitis related to AIDS presented with transient monocular visual loss. In eosinophilic vasculitis, infiltration of the vessel wall by eosinophils may lead to inflammation of the temporal artery that can precipitate an occlusive thrombus as well as

FIG. 3. Fluorescein angiography performed 70 minutes after vision had returned to baseline after the amaurotic episode described in Figure 1. A. Right eye, 1:01 minutes after dye injection, is normal. B. Left eye, 1:37 minutes, is normal. C. Right eye, 5:52 minutes. The patient has reported a second amaurotic episode of the right eye. Speckled hyper- and hypofluorescence are evident within the retinal vessels, consistent with interrupted blood flow. D. Right eye, 6:04 minutes. Same findings as in C. E. Left eye, 6:26 minutes, is normal. F. Right eye, 10:53 minutes. The patient has reported that vision in the right eye is returning to baseline. Speckled hyperfluorescence, representing decreased perfusion and concentration of fluorescein, is seen in some vessels (arrowheads). Homogeneous low level fluorescence, representing normal flow in the recirculation phase, is seen in other vessels (arrows). G. Right eye, 11:10 minutes. The patient has reported that vision in the right eye has recovered fully. Vessels appear normal. H. Left eye, 11:41 minutes, is normal.

FIG. 4. Histology of the temporal artery biopsy. Low-power view (A) shows inflammatory cell infiltration with focal disruption of the elastic lamina (arrow). L, lumen. High-power view (B) shows that the infiltrate is made up of chronic inflammatory cells mixed with a few giant cells as well as several eosinophilic leukocytes (arrows) located between the elastic lamina and the lumen of the vessel shown in A.

60
localized vasospasm (11–15). Transient visual loss believed to be the result of such localized vasospasm due to temporal artery inflammation has been reported previously (16).

Although FA evidence of sustained choroidal and retinal hypoperfusion and ischemia associated with persistent vision loss in eosinophilic vasculitis has been previously documented (17), the present case report is the first to angiographically demonstrate the complete course of altered blood flow due to retinal arteriolar vasospasm during an episode of transient monocular visual loss. Our patient is also a reminder that this manifestation may occur in eosinophilic vasculitis.

REFERENCES
Endovascular Techniques for Treatment of Carotid-Cavernous Fistula

Joseph J. Gemmete, MD, Sameer A. Ansari, MD, PhD, and Dheeraj M. Gandhi, MD

Abstract: Carotid-cavernous fistulas (CCFs) are abnormal arteriovenous communications in the cavernous sinus. Direct CCFs result from a tear in the intracavernous carotid artery. Indirect CCFs generally occur spontaneously and cause more subtle signs. Direct CCFs, which typically have high flow, usually present with ocular-orbital venous congestive features and cephalic bruit. Indirect CCFs, which typically have low flow, present with similar but more muted clinical features. Direct CCFs are always treated with endovascular methods. The goal is to occlude the fistula but preserve the patency of the internal carotid artery (ICA). Agents include detachable coils or liquid embolic agents delivered transarterially or transvenously. Arterial porous or covered stents are often used adjunctively. In rare cases, the ICA must be occluded. Indirect CCFs are only treated if symptoms are intractable or intolerable or if vision is threatened. The goal is to interrupt the fistulous communications and decrease the pressure in the cavernous sinus. The traditional approach has been transarterial embolization with liquid agents, particularly n-butyl cyanoacrylate (n-BCA). However, the multiplicity of arterial feeders and the low success rate in occluding indirect CCFs by the arterial route has led to a preference for transvenous embolization, most commonly via the inferior petrosal sinus. If that sinus is impassable, alternative routes include the pterygoid venous plexus, superior petrosal sinus, facial vein, or ophthalmic veins. The cavernous sinus is occluded with coils, liquid embolic agents, or both. The use of ethylene vinyl alcohol copolymer (Onyx), an agent that may be superior to n-BCA because it may allow better distal fistula penetration. However, more safety and efficacy data must be accumulated. When experienced interventionalists are involved, the success rate for closing direct fistulas is 85%–99% and for closing indirect fistulas is 70%–78%. Serious complications are relatively infrequent.


CLASSIFICATION

Carotid-cavernous fistulas (CCFs) are abnormal communications between arteries and veins of the cavernous sinus. They may be classified on the basis of etiology (traumatic or spontaneous), rate of flow (high or low), or angiographic architecture (direct or indirect). The most commonly used classification, based on architecture, was established by Barrow et al (1). It divides CCFs into 4 types depending on the arterial supply:

- Type A (direct): Direct communications between the internal carotid artery (ICA) and the cavernous sinus, usually with resulting high flow rates.
- Type B (indirect): supplied only by the dural branches of the ICA.
- Type C (indirect): supplied only by dural branches of the external carotid artery (ECA).
- Type D (indirect): supplied by dural branches of the ICA and ECA.

Direct CCFs may follow a traumatic tear of the cavernous segment of the ICA or rupture of an aneurysm within this segment of the ICA (2–4). The exact etiology of indirect CCFs is unknown, but they have been associated with pregnancy, sinusitis, trauma, and cavernous sinus thrombosis (5).

CLINICAL PRESENTATION

The classic presentation of direct CCFs is the sudden development of a triad of exophthalmos, cephalic bruit, and conjunctival congestion. Complete disruption of the wall of the ICA allows highly pressurized arterial blood to be...
directly transmitted to the cavernous sinus and ophthalmic veins, leading to venous hypertension. The principal manifestations of venous hypertension are ophthalmic (including proptosis, chemosis, conjunctival injection, and visual loss) but cranial nerve pareses, bleeding from the mouth, nose, or ears, intracranial hemorrhage, increased intracranial pressure, and steal phenomena are also seen (6,7).

Compared with direct CCFs, indirect CCFs have a gradual onset, typically with a milder clinical presentation. Indirect CCFs often do not demonstrate the classic triad of symptoms characteristic of direct CCFs. Patients have chronically red eyes because of tortuous arterialization of the conjunctival veins (Fig. 1), but a cephalic bruit is usually absent and exophthalmos is either mild or absent.

Unlike direct CCFs, most indirect CCFs improve spontaneously, and often all clinical manifestations will resolve without vascular intervention (8). However, patients with intractable headache, visual deterioration, elevated intraocular pressure refractory to medication, diplopia, or an intolerable cosmetic deformity are considered for endovascular treatment (9).

**IMAGING**

CT findings in direct and indirect CCFs include proptosis, enlargement of the extraocular muscles, enlargement and tortuosity of the superior ophthalmic vein, and enlargement of the ipsilateral cavernous sinus. MRI findings are similar to those seen on CT, with the addition of orbital edema and abnormal flow voids in the affected cavernous sinus (10). In the setting of a high-flow fistula and retrograde cortical venous reflux, MRI or CT studies may reveal dilatation of leptomeningeal and cortical veins. In patients with cerebral venous congestion, cerebral edema or hemorrhage may be encountered.

Digital subtraction angiography (DSA) is essential in confirming the diagnosis, classifying the CCF, and delineating the patterns of venous drainage. Such imaging is necessary in planning the optimal treatment approach for these often complex lesions. DSA frame rates of greater than 5 frames per second may aid in evaluating the morphology of high-flow fistulas. If it is not possible to identify the morphology of the fistula on selective high-frame rate ICA angiograms, specific maneuvers to slow flow through the fistula may be tried. The Mehringer-Hieshima maneuver consists of injecting the ipsilateral ICA and manual compression of the ipsilateral common carotid artery while filming at a slower film rate. With this maneuver, the fistula fills at a slower rate and allows for better delineation of the fistula site. The Huber maneuver involves injection of the ipsilateral vertebral artery with manual compression of the affected common carotid artery (11). With this maneuver, the fistula is opacified through a posterior communicating artery, if one exists.

**HISTORICAL TREATMENT**

Early treatment for direct CCFs consisted of various surgical approaches. In the 1930s, direct CCFs were “trapped” by ligation of the cervical and intracranial ICA. Trapping was followed by embolization using a number of different materials delivered by direct cavernous sinus exposure. In 1974, Parkinson et al (12) reported successful treatment of 9 of 11 patients with direct CCFs by surgical exposure and packing of the cavernous sinus with preservation of the ICA. In 1974, Serbinenko et al (13) reported the first case of successful embolization of a direct CCF from an endovascular approach using a detachable balloon.

In 1978, Debrun et al (14) reported the successful treatment of 12 of 17 direct CCFs with detachable balloons.

**FIG. 1.** Ophthalmic features of indirect carotid-cavernous fistula. A. Proptosis, ptosis, chemosis, and arterialization of the conjunctival veins of left eye before treatment. B. Resolution of ophthalmic abnormalities 8 weeks after endovascular treatment.
By the 1980s, detachable balloons were widely accepted as the treatment of choice for direct CCFs, even though most balloons used in the United States were imported. The U.S. Food and Drug Administration (FDA) had approved detachable balloons for peripheral vessel occlusion in 1981, but there were problems. The balloons would not detach or they detached inappropriately. They were withdrawn from the U.S. market in 1991. The FDA later approved detachable balloons for intracranial use (DSB; Boston Scientific-Target, Fremont, CA) in 1998, but they were withdrawn from use in the United States in 2003 because of balloon valve leaks.

CURRENT TREATMENT OF DIRECT CCF

A number of different endovascular treatment options for CCFs are currently available. The method chosen in a given patient depends on the anatomy of the fistula and operator or institutional preference.

The goal of treatment in direct CCFs is to occlude the site of communication between the ICA and the cavernous sinus while preserving the patency of the ICA. This can be accomplished with transarterial obliteration of the fistula with a detachable balloon, deployment of a covered stent across the area of the fistula, or obliteration of the ipsilateral cavernous sinus with coils or other embolic material. If the defect is large and cannot be repaired, the ICA may have to be sacrificed or trapped (Fig. 2).

Detachable Balloon

The standard treatment for a direct CCF in the United States had been transarterial obliteration of the fistula with a detachable balloon (15,16). The balloon could be directed by flow through the fistula into the cavernous sinus. Before detachment, the balloon could be inflated to a volume larger than the orifice of the fistula to prevent its retrograde prolapse into the ICA. This approach was relatively inexpensive, simple, and elegant (Fig. 3).

However, technical problems were occasionally encountered with detachable balloon embolization, including difficulty fitting the balloon through the rent in the artery, inability to convey the partially inflated balloon from the artery to the vein, and early detachment, deflation, or rupture of the balloon caused by contact with bone fragments (4,17). Problems with the balloon valve mechanism forced removal of this device from the U.S. market in 2003. It remains available for endovascular use in treating direct CCFs in other parts of the world.

Coils or Other Embolic Material

With the lack of availability of detachable balloons, transarterial or transvenous embolization with coils or other embolic material has become the mainstay of endovascular treatment of direct CCFs. Commonly used embolic agents include detachable platinum coils, n-butyl cyanoacrylate (n-BCA) (Trufill n-BCA; Cordis Neurovascular, Miami, FL), ethylene-vinyl alcohol copolymer (EVOH) (Onyx; ev3 Neurovascular, Irvine, CA), and silk.

Transarterial Embolization

The standard transarterial approach consists of placing a guiding catheter in the cervical carotid artery and advancing a microcatheter into the cavernous segment of the ICA. The microcatheter is selectively advanced across the tear in the carotid artery into the cavernous sinus. Using this microcatheter, embolic material is placed into the cavernous sinus. We prefer detachable platinum coils as they are easy to use and may be adjusted or even removed if the placement is not optimal (18). Liquid embolic agents such as n-BCA or Onyx may also be used to occlude the fistula (19,20). During transarterial embolization, a temporary balloon may be placed across the site of the tear to protect the parent vessel and prevent migration of embolic material distally into the cerebral hemisphere.

Transvenous Embolization

The transvenous route usually involves a posterior approach through the internal jugular vein and the inferior petrosal sinus (IPS) up into the cavernous sinus (21). If the IPS is occluded or absent, access to the cavernous sinus can be obtained from an anterior approach through the superior ophthalmic vein (SOV) via the facial vein (22). Other percutaneous transvenous approaches include the contralateral pterygoid plexus, superior petrosal sinus, and cortical veins (23,24). Less favored alternative approaches include a direct transorbital puncture of the cavernous sinus or access via the inferior ophthalmic vein (IOV) (25). We are aware of only one report of an IOV approach (26). Once cavernous sinus access is obtained, disconnection of the venous outflow from the feeding arteries at the level of the arteriovenous (AV) fistulas can be completed with detachable coils or liquid embolic agents.

Porous (Noncovered) Stent and Coils

CCFs caused by small tears in the ICA can be treated with detachable balloons or coils as described in the preceding sections. However, if there is a large arterial tear, the coils or balloons may migrate through the defect into the parent vessel, potentially causing cerebral vessel occlusion and stroke.

Dedicated self-expanding stents (Neuroform [Boston Scientific/Target Therapeutics Inc., Natick, MA] and Enterprise [Cordis Neurovascular, Miami, FL]) have recently become available for intracranial use. Although these stents are FDA-approved for coil embolization only of wide-necked intracranial aneurysms, they may be used to reconstruct severely injured intracranial arteries in direct CCFs (27).
FIG. 2. Schematic rendering of three endovascular methods of treating a direct carotid-cavernous fistula (CCF). A. A tear in the cavernous segment of the internal carotid artery (ICA) allows blood to escape directly into the cavernous sinus (CS). B. Occlusion by placement of a covered stent over the tear in the cavernous segment of the ICA. C. Placement of coils and a porous (noncovered) stent into the CS via a transarterial approach. The stent prevents prolapse of the coils into the parent vessel, the ICA. D. Occlusion of the fistula by placement of multiple coils within the parent vessel (ICA), resulting in its occlusion (long arrowheads). O, ophthalmic artery.

With this technique, a direct CCF with severe injury to the ICA can now be occluded while preserving the ICA.

Covered Stent
Placement of a stent covered with polyfluorotetraethylene (PTFE) or Gore-Tex (covered stent or stent graft) is another treatment option. It may immediately obliterate direct CCFs by placing an impermeable barrier across the site of fistula communication. In addition, it may decrease the risk of ischemic stroke by preserving the ICA (Fig. 4). There have been few reports of the successful application of a covered stent for the treatment of CCFs (28–30).
Currently, its use is restricted by the FDA to placement in the coronary artery after arterial rupture from balloon angioplasty/stent placement. The disadvantages of this stent are its stiffness and larger caliber, making it difficult to navigate into the distal ICA. Long-term safety data are lacking.

**Arterial Sacrifice**

Direct CCFs caused by extensive injury to the ICA may not be amenable to endovascular occlusion with preservation of the parent artery. In such circumstances, occlusion of the arterial segment bearing the fistula may be the only viable option. If time permits and the patient is able
to cooperate, a temporary balloon test occlusion of the ICA is carried out before permanent occlusion of the artery.

To prevent retrograde backflow of blood from the supraclinoid ICA into the fistula, the occlusion is initiated distal to the site of the suspected tear. Using several coils, the cavernous ICA is progressively occluded up to the arterial segment proximal to the fistula. This technique may be life-saving in a patient with extensive and unstable injuries. Recently, Hydrogel-coated detachable coils that swell on contact with blood have been introduced. Such coils may occlude vessels faster than bare platinum coils and decrease procedure and fluoroscopy times (31). The easy-to-deploy and fast acting Amplatzer vascular plug (AGA Medical Corporation, Golden Valley, MN) has been used in arterial sacrifice (32). However, navigation into the distal ICA is difficult.

**CURRENT TREATMENT OF INDIRECT CCF**

The goal of treatment for indirect CCFs is to interrupt the fistulous communications and decrease the pressure in the cavernous sinus. These goals can be accomplished by embolically occluding the arterial branches supplying the fistula (arterial approach) or by embolically occluding the cavernous sinus that harbors the fistulous communications (venous approach).

**Carotid Self-Compression**

Manual external carotid compression is an accepted treatment for indirect CCFs except in patients with retrograde cortical venous drainage and progressive visual decline.

This approach is particularly effective in patients harboring fistulas in the anterior cavernous sinus and in
those with acceptably low intraocular pressures and short duration of symptoms (33). The patient is instructed to sit in a chair or lie in bed and to compress the carotid artery and jugular vein with the contralateral hand for a period of 10 seconds, 4–6 times per hour. This approach is reported to result in clinical cure in 30% of patients (8).

Contraindications to manual carotid compression include hypertensive carotid sinus syndrome, atherosclerotic stenosis, ulceration of the cervical carotid artery, and history of cerebral ischemia, as patients with these anomalies cannot tolerate the transient occlusion of the ipsilateral internal carotid artery. This approach is also inappropriate if visual function shows progressive decline, intraocular pressure is intractably high, or there is intolerable periocular pain (33).

Transarterial Embolization

Transarterial embolization of indirect CCFs requires selective microcatheter placement distally within the arterial feeders to the fistula. An attempt is made to advance the microcatheter tip as close as possible to the point of fistulous communication. Once a satisfactory position of the microcatheter is achieved, an embolic agent is injected under fluoroscopic control. Although coils and particulate agents can be used, these agents cannot cause permanent occlusion of the fistula by themselves. The most commonly used agent for transarterial embolization is n-BCA (34).

n-BCA is a monomeric liquid adhesive whose polymerization time is controlled by the addition of iodized oil (Lipiodol). The advantages of n-BCA are easy delivery through the microcatheter, good penetration, rapid induction of thrombosis, and permanent occlusion after polymerization. A major disadvantage is rapid polymerization time (a few seconds), which causes it to stick to the microcatheter and protective balloons. n-BCA is approved in the U.S. for use in presurgical embolization of brain arteriovenous malformations (AVMs).

Onyx, another liquid embolic agent recently approved by the FDA for the preoperative embolization of brain AVMs, can also be used for transarterial embolization of indirect CCFs. A nonadhesive liquid embolic agent with a lava-like flow pattern, Onyx is supplied in ready-to-use vials in a dimethyl sulfoxide (DMSO) solvent with tantalum. Currently 6% (Onyx 18) and 8% (Onyx 34) concentrations are available in the U.S. When the mixture contacts aqueous media, such as blood, DMSO rapidly diffuses away from the mixture, causing in situ precipitation and solidification of the polymer, with the formation of a spongy embolus. The solidification occurs more slowly than that of cyanoacrylates, and because Onyx is nonadherent to the walls of vessels and microcatheters, its use allows prolonged injection times yet decreased chances of permanent microcatheter retention. Thus, it may allow better distal nidus or fistula penetration compared with cyanoacrylates and offer the possibility of venous sinus packing from a transarterial approach, which may be helpful in patients with previous occlusion of the draining venous structures. Use of Onyx for treating dural arteriovenous fistulas from a transarterial approach was recently described in two single-center cohorts (35,36).

Although transarterial embolization is a good treatment option, selective distal access into multiple tiny feeder vessels is often difficult or impossible and may require multiple sessions in a staged approach.

Transvenous Embolization

Transvenous embolization has become the preferred method of treatment of indirect CCFs. The advantages of this technique are its simplicity compared with transarterial methods, the ability to cure the fistula often in a single session and a high-long term success rate. The most

FIG. 5. Schematic rendering of the multiple dural sinus pathways that can be used to gain access to the cavernous sinus (CS) in transvenous occlusion of a carotid cavernous fistula: superior ophthalmic vein (SOV), inferior ophthalmic vein (IOV), inferior petrosal sinus (IPS), superior petrosal sinus (SPS), and middle deep temporal vein (MDTV).
The commonly used pathway for cannulation of the cavernous sinus is the IPS. If the IPS is inaccessible, the pterygoid venous plexus, superior petrosal sinus, facial vein, and SOV can be used (21–25) (Fig. 5).

Popular choices for embolic materials include coils, n-BCA, and Onyx, either in isolation or in combination. The advantages of coils are their radio-opacity, ease of use, and ability of redeploy or removal if the initial placement is not optimal (Fig. 6). However, a major disadvantage of coils is difficulty in achieving complete occlusion, especially in septated cavernous sinuses. Moreover, the reported rates of cranial nerve paralysis are higher with coils, probably because of their mass effect (37).

To overcome these disadvantages, liquid embolic agents are being increasingly used, either alone or in combination with coils (38,39). The liquid embolic agents can permeate different compartments, allowing complete occlusion of the fistula. In a series of 14 patients, Wakhloo et al (38) reported that n-BCA, used alone or in conjunction with coils, was safe and effective in treating complex indirect CCFs.

Onyx is emerging as a potentially useful liquid embolic agent in this setting. However, a dangerous feature of Onyx is its propensity to retrogradely fill other arterial feeders. Therefore, it must be used cautiously in an ECA that could harbor collateral vessels. Multiple angiograms

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**FIG. 6.** Treatment of an indirect carotid-cavernous fistula (CCF) with intracavernous placement of a porous (noncovered) stent and coils. A. T2 axial MRI shows proptosis of the left eye (arrowhead), engorgement of the intraconal fat (arrow), and enlargement of the extraocular muscles. B. Lateral common carotid angiogram of the same patient demonstrates filling of the cavernous sinus (CS) and inferior ophthalmic vein (IOV) from branches off the internal maxillary artery (IMAX) and internal carotid artery (ICA). There is a small cavernous carotid aneurysm (A). C. Lateral external carotid angiogram with a balloon inflated in the proximal left ICA (arrowhead) shows filling of the CS and IOV from branches of the left IMAX. D. Lateral unsubtracted spot fluoroscopic image shows a porous stent (small arrowheads) within the cavernous segment of the ICA and coils in the cavernous aneurysm (A) in the region of the fistula. A microcatheter is seen in the inferior petrosal sinus (IPS). E. Lateral unsubtracted spot fluoroscopic image shows a microcatheter coursing from the IPS through the CS with its tip in the IOV before coil embolization of the venous outflow of the fistula. A porous stent is seen within the cavernous segment of the ICA (arrowheads) with coils in the cavernous aneurysm (A). F. Lateral angiogram after coil embolization of the venous outflow of the indirect CCF and porous stent-assisted coiling of the cavernous aneurysm shows occlusion of the fistula. Small arrowheads demarcate the stent.
can be obtained during the infusion to monitor the progress of the embolization. Although its use in the treatment of CCFs will probably increase, only a few case reports describe its successful use from a transvenous approach in treatment of indirect CCFs (39). (See also articles by Bhatia et al (40) and Gandhi et al (41) and Editorial (42) in this issue of the Journal.)

TREATMENT SUCCESS RATES

The reported cure rate with balloon embolization of direct CCFs is 88%–99% (4,43,44). Kobayashi et al (44) treated more than 200 traumatic CCFs with complete occlusion of the fistula in 99% and preservation of the parent artery in 88%. Gupta et al (46) achieved complete occlusion in 86.3%, near total occlusion in 11.0%, and ICA preservation in 98%. Moron et al (27) achieved successful obliteration of 6 direct CCFs by using stent-assisted coil placement. Gomez et al (30) demonstrated occlusion of direct CCFs and preservation of the ICA in 7 patients with PTFE-covered stents. The risks are ICA occlusion and worsening of an ocular motor cranial nerve palsy in 10%–40% of patients (4,40,47,48).

The reported cure rate for indirect CCFs is 70%–78% with a complication rate of 5% (9,49,50). Improvement of the patient’s symptoms has been reported in 20%–30% of patients without a complete angiographic cure.

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Opsoclonus Caused by Diphenhydramine Self-Poisoning

We report a patient who developed opsoclonus together with coma, seizure, autonomic disturbance, and rhabdomyolysis from diphenhydramine overdose. This is the second case report of opsoclonus in this setting (1).

A 22-year-old man was found unconscious in bed. Shortly thereafter, he developed a generalized seizure. In our hospital, his body temperature was 36.6°C, blood pressure was 142/90 mmHg, and pulse rate was 153 beats/min. He was unresponsive to painful stimuli. His pupils were dilated and sluggishly reactive to direct light. He had rapid conjugate oscillations of the eyes in the horizontal, vertical, and rotatory planes interpreted as opsoclonus.

Abnormal blood test results included hematocrit of 53.1%, white blood cell count of 22,900/mm³, pH of 6.837, anion gap of 33 mEq/L, serum creatinine of 1.32 mg/dL, and creatine kinase of 292 IU/L. Results for plasma glucose, electrolytes, and ammonia were within normal ranges.

The Triage Drugs of Abuse Panel (BIOSITE, Inc., San Diego, CA) detected no benzodiazepines or tricyclic antidepressants or their metabolites in the urine. Electroencephalography showed diffuse beta waves without epileptiform activity. Results of brain MRI and lumbar puncture were normal.

Several hours after the patient’s admission, his serum creatine kinase level rose to 72,312 IU/L, and oliguric acute renal failure occurred. At this time, a family member found empty diphenhydramine packages in the patient’s room, suggesting self-poisoning with this agent.

We treated the patient with intravenous fluids, furosemide, and 800 mg valproic acid daily. Opsoclonus disappeared on the second hospital day. The patient’s level of consciousness returned to normal in tandem with recovery of renal function over several days. There were no residual clinical deficits.

After recovery the patient confirmed that he had ingested 3.3 g diphenhydramine in a suicide attempt after conflict with his fiancee. He had been taking the diphenhydramine tablets for insomnia and had purchased multiple packages from several drugstores. High-performance liquid chromatography (HPLC) analysis of the patient’s serum 10 hours after he had ingested the diphenhydramine disclosed a serum concentration of 2.61 mg/mL. (In healthy young adults, the mean maximal serum concentration after ingestion of 50 mg diphenhydramine orally is 82.2 ± 31.5 ng/mL [2].)

Diphenhydramine is a first-generation antihistamine that can have both excitatory and inhibitory effects on the central nervous system. Its anticholinergic activity can cause autonomic disturbance (3). The previous report of opsoclonus in diphenhydramine poisoning is very similar to ours, in that the patient suffered from opsoclonus, cerebellar ataxia, and mental status changes. The patient confirmed ingestion of 2 g diphenhydramine, and HPLC analysis of the patient’s urine confirmed the diagnosis (1). Two reports have described single cases of oculogyric crisis, spasmodic conjugate ocular deviations usually in an upward direction (4,5).

Opsoclonus is found mostly in association with viral or paraneoplastic encephalitis, but it may be observed in patients intoxicated with agents such as lithium and organophosphates (6). Lithium may affect the function of glycinergic omnipause neurons, and organophosphate poisoning may affect cholinergic inputs from the pedunculopontine to the fastigial nucleus (6). We speculate that the opsoclonus seen in our patient was caused by the anticholinergic activity of diphenhydramine. Interestingly, oculogyric crisis has been reported not only in an overdose of diphenhydramine but also in an overdose of cetirizine, a second-generation antihistamine with anticholinergic effects (7).

In light of the fact that diphenhydramine is widely available, clinicians should recognize its potential to cause opsoclonus.

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See-Saw Nystagmus in a Patient with Wallenberg Syndrome

See-saw nystagmus (SSN), a form of disconjugate nystagmus in which one eye elevates while the other depresses, is most commonly found in patients with large tumors in the region of the diencephalon or mesencephalon (1–3). Trauma, multiple sclerosis, and achiasma may also produce it (3,4). We describe a patient who had SSN as part of a dorsolateral medullary infarct (Wallenberg syndrome) without clinical or imaging evidence of a lesion in the diencephalon or mesencephalon.

A 61-year-old man reported acute ataxia. Examination disclosed a primary position right hypertropia, left ptosis and miosis, and pendular see-saw nystagmus that increased on left gaze. The ascending eye intorted and the descending eye extorted. He also had left facial hypesthesia, right extremity loss of pain and temperature sensation, and gait ataxia.

Complete blood count, erythrocyte sedimentation rate, and glucose, urea, and electrolyte levels were normal. Brain MRI showed an acute infarction confined to the left dorsolateral medulla and inferior cerebellum (Fig. 1).

Although SSN is considered to be highly localizing to the diencephalon or mesencephalon, there are some exceptions (5). The mechanism of this nystagmus is still not known. Some authors hypothesize a disturbance in visual input because of its frequent association with chiasmal and parasellar lesions (5). But visual loss need not be present, suggesting dysfunction of the rostral brainstem (6), perhaps in the interstitial nucleus of Cajal (INC), a small collection of neurons located adjacent to medial longitudinal fasciculus (MLF) in the midbrain tegmentum (6).

Given that our patient had a lesion apparently confined to the medulla and cerebellum the physiopathologic origin could be related to dysfunction of the vestibular nucleus or the MLF. These pathways have direct connections with the third and fourth cranial nerve nuclei via the MLF and the INC. We suggest that a lesion impairing the function of that circuitry could cause SSN.

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FIG. 1. Axial diffusion MRI shows left dorsolateral medullary (small arrow) and inferior cerebellar hemispheric (large arrow) high signal consistent with acute infarction (A) and a normal mesencephalic signal (B).
Another Case of Paroxysmal Tonic Downgaze in Infancy

Two years ago, Wolsey and Warner (1) reported in this journal on two healthy infants with brief episodes of downgaze followed by abnormal body movements. They called this condition “paroxysmal tonic downgaze” and considered it idiopathic and transient. We extend their report by describing a 2-month-old healthy boy presenting with an episodic downward gaze disturbance (Fig. 1).

Born at term after an uneventful delivery and normal development, he was transferred for possible “seizures” from another hospital. The spells had started 7 days before presentation, coincident with a diagnosis of a new upper respiratory tract infection. We observed many spells per day that lasted between 10 and 90 seconds without any impairment in consciousness and seemed to occur more frequently when he was supine or upon awakening but never in an upright position or during sleep. They did not appear to follow touching or shaking. Longer spells were associated with stiffening of the right upper extremities.

Ophthalmologic examination disclosed that he fixed and followed equally with each eye. He had normal alignment and full extraocular movements without nystagmus. Neurologic examination showed slightly reduced muscle tone but normal muscle strength and deep tendon reflexes. There was no ataxia.

The child underwent MRI and an electroencephalogram (EEG) because of a report of hydrocephalus and seizures in very similar downgaze episodes in children aged 2 to 8 months (2) who later showed severe developmental disabilities. Results of these studies were normal.

Because we could not entirely exclude opsoclonus-myoclonus syndrome, we undertook evaluation for neuroblastoma with ultrasound of the abdomen, urine for vanillylmandelic acid levels, and iodine-131 metaiodobenzylguanidine (MIBG) scanning (3). Results of all studies were negative.

The episodes began to decrease in frequency spontaneously 1.5 months after they began and resolved within 3 months. He did not develop any neurologic problems in the subsequent 18 months and has had normal development except for a slight delay in expressive language and a mild attention deficit.

The pathogenesis of this transient gaze disturbance is not understood. Some observers have hypothesized that it may be the result of immature myelination of the corticomesencephalic vertical gaze pathways (4). Its transient nature, especially in older infants, may result from temporary failure of cortical compensation when a stressor such an illness is present (5).

Our experience reinforces the idiopathic and transient nature of this condition. Even so, this manifestation is frightening. Because more serious conditions cannot be entirely excluded, imaging and an EEG cannot be avoided.
Letters to the Editor

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Leber Hereditary Optic Neuropathy Associated with Malabsorption Syndrome After Bariatric Surgery

We report a patient who developed bilateral visual loss from Leber hereditary optic neuropathy (LHON) in conjunction with chronic malabsorption consequent to bariatric surgery.

A 31-year-old man reported visual loss in his left eye and, 2 weeks later, in his right eye. His vision gradually worsened down to finger counting at a distance of 1 m, and he was admitted to the hospital for study. He had undergone vertical banded gastroplasty for morbid obesity 3 years earlier. He smoked 10 cigarettes/day and drank a few alcoholic drinks on weekends. Past ocular history was negative. Family history was remarkable for a maternal cousin with a history of unexplained poor vision since childhood.

On our examination, visual acuity was 20/40 in the right eye and 20/200 in the left eye. There was a dense central scotoma in the visual field of the left eye and a pale optic disc in that eye. There was an afferent pupil defect on the left. No other ocular findings were detected, and results of the neurologic examination were unremarkable.

Results of extensive hematologic, serologic, and cerebrospinal fluid studies were all normal or negative except for decreased serum levels of vitamin E at 3.4 mg/mL (normal range 5-20 mg/mL), borderline serum levels of vitamin B12 and folate (253 pg/mL and 3.6 ng/mL, respectively), and increased mean corpuscular volume at 101 fl. Results of CT and MRI of the brain and orbits were normal. Pattern-reversal visual evoked potentials revealed marked bilateral delay with P100 latencies of 130.8 ms from the right eye and 156.3 ms from the left eye.

The patient received treatment with 1,000 mg/day methylprednisolone intravenously for 5 days, as well as oral vitamin B complex and vitamin E. There was no improvement in vision during his hospitalization.

Genetic testing, performed at Public Foundation of Genomic Medicine (Santiago de Compostela, Spain), showed a homoplasmic mitochondrial DNA (mtDNA) mutation at position 11778A, confirming the clinical diagnosis of LHON. On a 10-month follow-up, clinical examinations showed no substantial changes.

We have described a young man with a LHON mtDNA mutation and a history of moderate alcohol and tobacco abuse who developed subacute bilateral optic neuropathy in the setting of chronic malabsorption (multiple vitamin deficiency) induced by bariatric surgery.

Epigenetic factors are reported to contribute to the clinical expression of LHON mtDNA mutations, including tobacco smoking, alcohol consumption, uncontrolled diabetes, ethambutol use, and antiretroviral therapy (1). There are similarities between the optic neuropathies of LHON, vitamin B1 deficiency, and vitamin B12 deficiency, suggesting that abnormalities of adenosine triphosphate levels might be the common underlying pathogenetic mechanism (2). In our patient, tobacco smoking and alcohol consumption may have contributed. Visual loss began after bariatric surgery, perhaps in the context of malabsorption.

Asymptomatic 11778 mtDNA LHON carriers frequently show manifestations of optic nerve impairments in relation to environmental factors (3), just as mutations in the 12S rRNA gene of the mitochondrial genome increase susceptibility to the ototoxicity of aminoglycoside antibiotics (4). Three cases of LHON in subjects who also had low serum vitamin B12 levels at the time of symptom onset have recently been reported (5). Taken together, these observations suggest that optic neuropathy in patients carrying a primary LHON mtDNA mutation may be precipitated by vitamin deficiency.

Patients who have undergone bariatric surgery show multiple biochemical abnormalities consistent with malabsorption, including low serum levels of vitamin B12, vitamin D, vitamin E, calcium, copper, or zinc. Some patients develop encephalopathy, optic neuropathy, posterior lateral myelopathy, acute polyradiculoneuropathy, and polyneuropathy. Perhaps a positive family history of visual loss should prompt mtDNA investigations before bariatric surgery is considered.
Perinatal Head Tilt in Congenital Superior Oblique Palsy

Congenital superior oblique palsy is often misdiagnosed as congenital muscular torticollis in the young child with a persistent unilateral head tilt (1,2). One of the distinguishing features of these conditions is said to be the later time of onset of the torticollis in congenital superior oblique palsy (1,2). However, we recently examined a patient who used a compensatory head tilt for binocular fusion almost from birth, demonstrating that a perinatal head tilt can result from congenital superior oblique palsy.

A 2½-year-old girl was referred for possible strabismus. According to her parents, she had maintained a large right head tilt since birth. An orthopedist had diagnosed congenital muscular torticollis and treated her with passive stretching exercises without improvement. She was neurodevelopmentally normal and had no family history of torticollis or strabismus.

On our examination, she had normal optokinetic responses and pupillary responses to light, and no fixational preference with either eye. She had no restriction to passive neck rotation, but maintained a right head tilt of 25 degrees with a small right head turn. She had 6 prism-diopters of left hypertropia that increased to 30 prism-diopters in right gaze and to 12 prism-diopters in left head tilt. She had no detectable hyperdeviation in left gaze or in right head tilt. Retinal examination showed 3+ extorsion of the left eye. Brain and orbit MRI showed selective hypoplasia of the left superior oblique muscle (Fig. 1). A left inferior oblique muscle recession produced resolution of the torticollis.

A review of old photographs revealed an interesting and unrecognized phenomenon. Beginning at 2 weeks of age, she always leaned to the right side when sitting or being held, allowing gravity to tilt her head and trunk to the right (Fig. 2). She maintained this consistent body posture until 6 months of age, at which time her trunk straightened and her head remained tilted (Fig. 2). She also maintained a slight right head turn and a gaze preference to the left. While awake and during sleep, her head tilt resolved in the supine position. For confidentiality reasons, her parents requested that these photographs not be published.

Congenital muscular torticollis is said to be present from birth or shortly thereafter, whereas ocular torticollis is said to appear later, when the child develops sufficient head control to maintain an abnormal head position for fusion (1,2). Duke-Elder and Wyber (1) and von Noorden (2) stated that the head tilt associated with congenital superior oblique palsy may not develop until 18 months of age.

Our patient belies this clinical axiom by showing that congenital superior oblique palsy can be associated with a head tilt that develops within the first month of life. In the
absence of head control, our patient allowed gravity to passively tilt her body in the compensatory direction to optimize utricular input for vertical fusion. By 6 months of age, head control had become established, allowing her to straighten her trunk while maintaining her head in its tilted and slightly turned position. Mocan et al (3) documented a right gaze preference in a 3-week-old infant with transient left sixth cranial nerve paresis, suggesting that active binocular visual processing was already producing a robust drive to fuse.

This patient demonstrates that infants with congenital superior oblique palsy can use gravitational body tilt to compensate for vertical diplopia shortly after birth. For this reason, superior oblique palsy should not be ruled out as the cause of a history of unidirectional head tilt that begins within the first month of life.

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Lanning B. Kline, MD.

Scope: Although it has been almost 30 years since the first edition of this “nuts and bolts” neuro-ophthalmic guide, it remains a valuable resource. The spirit of the original text authored by Frank Bajandas, MD (now deceased) has been maintained by Lanning Kline, MD, in this 6th edition.

It is true to its mission to be “A readable compendium of ‘no-nonsense’ neuro-ophthalmology,” and the format remains easy to read and generously supplemented by figures, illustrations, anatomic diagrams, and summary tables. This edition updates the previous one with new information, expanded references, 28 tables, 138 figures, and an enjoyable quiz of 33 visual field exercises of various levels of difficulty and complexity. In addition, there are revised and updated chapters on supranuclear and internuclear gaze pathways (Mark F. Walker, MD), headache (John E. Carter, MD), eyelids (Jennifer T Scruggs, MD), visual fields, and nystagmus and related ocular oscillations.

Strengths: This book is easy to follow and quick to read and thus enduringly popular with residents and medical students. The outline format and outstanding and creative use of black and white cleanly drawn illustrations, figures, anatomic diagrams, and tables distinguish it from drier review books.

Weaknesses: The outline format requires the reader to have some basic understanding of the material. Brief coverage occasionally leads to uneven depth in some sections. Although the outline format makes for easy reading, filling in the gaps between the bullet items might be a challenge for the beginner. In some chapters the abbreviations are not clearly identified. These are, however, minor quibbles.

Recommended Audience: This edition will, like its predecessors, be useful for general practitioners and especially residents and fellows in ophthalmology, neurology, and neurosurgery who seek a handy reference.

Critical Appraisal: This book remains an invaluable review manual for residents, fellows, and clinicians on topics of clinical interest in neuro-ophthalmology. I recommend it often to my own residents and fellows when they ask me for an easy-to-read, affordable, review book.

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Rapid Diagnosis in Ophthalmology: Neuro-Ophthalmology

Jonathan D. Trobe, MD.

Scope: This ready-to-go, single-authored manual slides comfortably into a busy clinician’s pocket. It contains an abbreviated storehouse of common disorders affecting both the visual and ocular motor systems that reflects Dr. Trobe’s extensive experience.

Strengths: The format is well organized and standardized into key facts, common findings, differential diagnosis, ancillary tests, treatment, and prognosis. The information is provided in a bulleted form with highlights and lively color photographs, neuroimages, and graphic illustrations of eye movement disorders.

Weaknesses: If the reader is looking for a discussion of pathogenesis or a justification of concepts and recommendations, it is not found here. There are no references. Quantitative data are rounded off, and the outline style forgoes discussion. Judgment is implied for the use of ancillary testing, and perspective is limited.

Recommended Audience: In providing a ready reference for those seeking quick answers in a fast-paced practice, this work is on the mark. The presentation is concise, accurate, and stimulating. It would also be very useful for interested students and beginning residents in both ophthalmology and neurology.

Critical Appraisal: As a frontline text for rapid organization and direction, this is a highly useful pocketbook. Neuro-ophthalmologists will also appreciate it as a generator of referrals.

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Neuro-Ophthalmology [Blue Book of Neurology Series]

Desmond P. Kidd, MD, Nancy J. Newman, MD, and Valerie Biousse, MD.

Scope: This text is part of the series of Blue Books designed to summarize important topics in neurology. It serves as a neuro-ophthalmology primer covering a broad range of topics. The text is 375 pages, multi-authored, and full of color illustrations and numerous radiographs.

The book is divided into 14 different chapters with one or more authors each. The chapter title page includes an outline and several key points that serve to emphasize important and current topics. Within each chapter are extensive titles and subtitles that serve to organize the chapters in a fairly standardized fashion. The editors have succeeded in having the authors accomplish the goal of the text, namely, to provide a general summary on the topic while emphasizing contemporary information.

Strengths: Numerous experts in the field author the chapters. For instance, there are chapters on optic nerve tumors by Neil Miller, MD, hereditary optic neuropathies by Nancy Newman, MD, transient vision loss by Valerie Biousse, MD, and optic neuritis by Desmond Kidd, MD, and Gordon Plant, MD. The authors uniformly succeed in providing concise and up-to-date summaries emphasizing the most important information. They have done an admirable job of making the text fairly comprehensive despite the manageable size of the book. The initial chapter on anatomy and diagnostic techniques is an excellent resource and the type of material that I would recommend copying and distributing to residents in ophthalmology and neurology as they begin to learn neuro-ophthalmology. Other notable chapters include those on transient monocular vision loss and hereditary optic neuropathies. The chapter on pupillary disorders provides an excellent summary of pupillary anatomy and physiology. Finally, the chapter on cortical visual disorders is a well-written rendering of a difficult topic. The illustrations and figures are all produced in a high-quality fashion and include excellent descriptive legends.

Weaknesses: There are no glaring weaknesses except for some unevenness in page distribution for certain topics. For instance, the chapter on acquired ocular motility disorders and nystagmus contains less than 1 page about third cranial nerve palsy. Each chapter uses references to a different degree, sometimes leaving the reader to wish for more extensive access to the primary literature. Several figures would have benefited from more careful labeling and arrows to highlight pathologic lesions.

Recommended Audience: This book is well-suited to residents in training in neurology and ophthalmology and practitioners who are interested in a concise and manageable read and an update on contemporary thinking in this field.

Critical Appraisal: This is an excellent textbook with superb authors, high-quality figures, and a comprehensive review and update. Even an experienced neuro-ophthalmologist would enjoy reading the opinions of experts.


Jaypee Brothers, New Delhi, India, 2008.

Scope: This is a pictorial atlas of neuro-ophthalmic findings accompanied in many cases with imaging and text describing the condition and references about the condition. As in any atlas, the book has numerous illustrations, most of high quality. The book is organized into afferent disorders, efferent disorders, congenital disorders, infective disorders, vascular disorders, tumors, phacomatoses, and miscellaneous disorders. Disorders are alphabetically arranged. Each disorder starts with general information on clinical manifestations, evaluation, and treatment followed by references. The text is accompanied by color photographs and imaging. The last section consists of 36 multiple choice questions about conditions covered in the atlas with explanations of the answers. The index is fairly complete.

Strengths: Although this is a multi-authored atlas, the style is consistent. Its major strength is that it is readable, concise, and well illustrated.

Weaknesses: Conditions that do not lend themselves well to illustration are less well represented. For example,
omissions include tonic pupil, horizontal gaze palsies, third cranial nerve palsy due to aneurysm, and nystagmus.

Some images are inappropriate. For example, in discussing anterior ischemic optic neuropathy (AION), the authors chose an angiogram of the carotid arteries in an individual with transient monocular blindness. Some references are not relevant. For example, in the discussion of arteritic ischemic optic neuropathy, the authors use a reference dealing with the nonarteritic variant of this condition.

In the illustrations, identifying arrows would have been helpful. The illustration of the three-step test could have benefited from the use of labels.

Recommended Audience: Medical students, ophthalmologists, neurologists, and neurosurgeons who want a quick take will find this atlas useful. Neuro-ophthalmologists will find it useful in teaching students.

Critical Appraisal: This atlas is a fine introduction to neuro-ophthalmic conditions, particularly those that can be summarized with brief text and illustration. In future editions, the authors wish to include more eye movement disorders with perhaps a CD or references to where eye movement videos can be found.

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Salt Lake City, Utah

The Pseudotumor Cerebri Syndrome: Pseudotumor Cerebri, Idiopathic Intracranial Hypertension, Benign Intracranial Hypertension, and Related Conditions

Ian Johnston, PhD, Brian Owler, PhD, and John Pickard, MD.

Scope: Written from a neurosurgical perspective, this monograph provides an authoritative and comprehensive review of conditions causing increased intracranial pressure, including historical, clinical, experimental, and treatment perspectives.

Strengths: The neurosurgical approach to increased intracranial pressure is detailed, thoughtful, and thorough. An excellent historical and nosological perspective on conditions causing raised intracranial pressure is provided. There is a wonderful section on history of the condition. In this section, the authors weave in details of seminal studies, nosology, and advances in neuroimaging.

The chapter on clinical investigations is excellent and thoughtful. A historical perspective is provided. The section on continuous cerebrospinal fluid (CSF) pressure monitoring is superb as are the other neurosurgical and neuroradiologic sections. This chapter has much useful information and itself is worth the price of the book.

The sections on treatment using corticosteroids, subtemporal decompression, and CSF shunting are especially informative, and these discussions are among the best available. The chapter is comprehensive in detail except for a deficiency with regard to perimetric outcomes. Authoritative strategies for treatment with an approach biased toward neurosurgical techniques are given; the recommended strategies are certainly not mainstream neuro-ophthalmology but make for interesting reading.

Weaknesses: There is an unbalanced emphasis on nosology, resulting at times in a disorganized grouping of conditions causing elevated intracranial pressure. The discussion of the clinical syndrome is incomplete owing to a lack of emphasis on series with prospective data collection. Treatment decisions are somewhat more driven by neurosurgical interventions than the more widely used perimetric and optic disc observations.

The authors define pseudotumor cerebri syndrome (PTCS) broadly, including any condition that causes impairment of CSF absorption at the point of transfer of the fluid from subarachnoid space to dural venous system. Although this makes theoretical sense, the authors admit that this mechanism remains unproven. Moreover, alternative mechanisms are not presented in detail.

The authors propose that there is a close analogy between PTCS and hydrocephalus. They stretch this to include communicating hydrocephalus and infantile macrocephaly. Their argument is speculative, interesting, and provocative but unconvincing. Although generally thorough, the chapter on clinical manifestations is hindered by lack of data from published prospective data collections that give more accurate estimates. For example, the authors quote a 10% frequency of tinnitus, which is 60% in prospective series that ask patients if they have this symptom.

The chapter on treatment suffers from the inclusion of a diverse number of conditions that fall under their rubric of PTCS. Pregnancy is included as a cause, although case-control studies have shown otherwise.

Recommended Audience: Neuro-ophthalmologists, neurosurgeons, and neurologists with an interest in the PTCS and idiopathic intracranial hypertension will find this book useful.
Book Reviews

Critical Appraisal: This is a useful reference text. It has a very neurosurgical flavor, which is not surprising given the background of the authors. The sections on history, intracranial pressure monitoring, and neurosurgically based treatments are especially well done. Those interested in disorders of increased intracranial pressure will want this monograph on their shelves.

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Rapid Diagnosis in Ophthalmology: Pediatric Ophthalmology and Strabismus

Mitchell B. Strominger, MD.

Scope: This is one of a series of 6 pocket-sized books intended to serve as reference guides. It is organized into 14 chapters covering amblyopia, infectious diseases, inflammatory conditions, congenital anomalies, esotropia, exotropia, vertical misalignments, thyroid eye disease, orbital fibrosis, myasthenia gravis, congenital nystagmus, and spasmus nutans.

The chapters review up to 18 diagnoses in succinct outline format covering key facts about each disease condition, its clinical findings, ancillary testing, differential diagnosis, treatment, and prognosis. Most conditions are covered within 1 page of bulleted outline text, and all but 5 are accompanied by clear color photographs, many of which have been borrowed from Taylor and Hoyt’s extensive text on pediatric ophthalmology and strabismus.

Strengths: This is an easy-to-read and easy-to-use book that covers more than just the basics of the most common conditions in pediatric ophthalmology. The sections on TORCH infections, allergic eye disease, retinopathy of prematurity (ROP), child abuse, and the phakomatoses are particularly well written.

Weaknesses: As with any book of this nature, the weaknesses are primarily in what has been left out, such as Stargardt disease, idiopathic intracranial hypertension, hereditary optic neuropathies, and de Morsier syndrome. Information is sometimes sparse and always unreferenced. Many of the photographic pages include only one image, with large amounts of empty space that could have been used for additional pertinent figures or clarifying text.

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Oxford Handbook of Ophthalmology

Alastair K. O. Denniston and Philip I. Murray, MD.

Scope: This is a reference for practicing ophthalmologists and residents in training. It aims to be somewhat comprehensive yet portable. The first 2 chapters on examination and test interpretation are really more applicable for those early in their practice of ophthalmology. The second major section of the book addresses the more common diagnoses associated with different sections of the eye, orbit, and central nervous system. There are small discussions of the diagnoses within each of these entities. The last section of the book is essentially an appendix with some miscellaneous information.

Strengths: The authors accomplish the goal to produce a book that can be referenced easily throughout the day, during consults, patient encounters, and rounds yet be comprehensive. There are helpful hints in the examination and test interpretation sections. The diagnosis section hits most important topics. The references to evidence are beneficial. This manual is superior to many other eye manuals in that it has more than just treatment options.

Weaknesses: As with most reference books, there is never enough information. Some of the anatomy and physiology text seemed out of place except in a reference for beginning residents, which just adds volume to an already voluminous book. The appendix and miscellaneous section also had information that is misplaced in a reference text.

Recommended Audience: This book is aimed more to residents than to seasoned clinicians, especially the beginning chapters and anatomy discussions. However, it does have valuable information for those in practice.

Critical Appraisal: This reference is useful especially for residents and provides a little more information than the traditional eye manuals.
Garner and Klintworth’s Pathobiology of Ocular Diseases, 3rd Edition

Gordon K. Klintworth, PhD, and Alec Garner, MD, PhD.

Scope: This two-volume set encompasses current knowledge of anatomic pathology, cell biology, molecular biology, and biochemistry of ocular disease. Numerous authors provide a multidisciplinary depth of information unmatched in current eye pathology texts. The book is organized by mechanisms rather than anatomic areas. Unification of the chapter format is achieved from a set outline permitting easy transition between chapters despite the multiple writers. A great deal of space has been allocated for detailed presentations of etiologic aspects of various disease processes. The intended audience includes ocular pathologists, neuropathologists, ophthalmologists, and scientists working in disciplines such as immunology, genetics, and cell biology.

Strengths: This unique textbook is designed to promote the understanding of disease processes. It is meticulously referenced and contains an enormous amount of detail concerning the genetics and cell biology of ocular disease. Most chapters provide interesting historical information, superb pathophysiological explanations, and exhaustive tables. The outstanding quality of many chapters such as Genetic Disorders of the Cornea, authored by Klintworth, exemplifies the expertise of the authors.

Weaknesses: Illustrations, all black and white, vary in quality. The ambitious attempt to explore the pathogenesis of so many topics has taken some authors to their limits and accounts for some omissions. For example, tear lipocalin, a siderophore binding protein, is overlooked in the discussion of microbial competition for iron in the tear film. To stay current, the work will require frequent updates.

Recommended Audience: This is an excellent reference textbook for scientists and pathologists who work with the eye. The book’s comprehensive nature may be overwhelming as a primer for residents training in ophthalmology, but the book will be a superb reference source for them.

Critical Appraisal: This book is an outstanding contribution to the field of ophthalmic pathology. It provides a comprehensive overview not found in any other work in our discipline.


Barbara Zoltan, MA, OTR/L.

Scope: This textbook focuses on the assessment and rehabilitative management of visual and neurocognitive impairments commonly seen after stroke and traumatic brain injury.

The first section briefly discusses general principles and other factors that guide overall management. Rehabilitative treatment approaches, including the Bobath concept and neuro-developmental treatment (NDT), are reviewed as well as other theoretical models. A general discussion of observational assessment and testing strategies follows. The second section forms the majority of the text. Specific assessment tools and treatment strategies for impaired vision and ocular motor function, visual neglect, apraxia, agnosia, attention, and executive cognitive function are described in detail.

Strengths: Clinically relevant assessment tools are described in detail and can be applied to clinical practice. Specific treatment strategies for each impairment are helpfully classified as restorative or adaptive and organized in outline form for easy reference.

Weaknesses: This edition addresses stroke and traumatic brain injury together under the umbrella of acquired brain injury. Because these disorders are distinct and associated with different impairments, the author is obliged to jump back and forth between patient populations. The book does not address the prevalence, prognosis, and time course of recovery of the various impairments. Research supporting the efficacy of the proposed treatment strategies is also not fully explored. The text is heavily referenced, but given its broad content, the absence of contributing authors with expertise in neuropsychology, speech language pathology, ophthalmology, and optometry is a problem.

Recommended Audience: Rehabilitation specialists working with traumatic brain injury and stroke patients will find the book a practical resource for clinical practice.
Critical Appraisal: The author’s background is in occupational therapy and much of the book’s content and perspective seems to be geared to practicing therapists. Rehabilitation professionals will find the material well organized and clinically relevant. Because many of the assessment tools and treatment strategies specifically fall within the realm of the occupational therapist, physicians will not find the content particularly applicable to their practices.

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Susana Martinez-Conde, PhD, Stephen L. Macknik, PhD, Luis M. Martinez, PhD, Jose-Manuel Alonso, PhD, and Peter U. Tse, PhD, Editors.

Scope: This is the second volume of a series entitled Visual Perception. It is based on the symposia presented at the European Conference on Visual Perception (ECVP) 2005, held in Spain.

The book is divided into four sections, each consisting of a collection of selected papers covering a topic in vision science. The first section, entitled The Role of Context in Recognition, deals with recognition of higher-level visual objects and explores how top-down influences and context-based information affect object recognition. The second section, entitled From Perceptive Fields to Gestalt: a Tribute to Lothar Spillmann, includes papers presented at the special symposium in honor of one of the founders of ECVP, as well as the plenary lecture of Dr. Spillmann. The third section, entitled The Neural Basis for Visual Awareness and Attention, brings together five articles that cover aspects of visual awareness, including blindsight, binocular rivalry, attention, and visual masking. The fourth section, entitled Cross-Modal Interactions in Visual Perception, contains articles that investigate issues ranging from exploration of synesthesia to investigations on how information from auditory and visual modalities is integrated into a unique percept.

Strengths: The quality of articles is consistently high. The authors are well-respected researchers. Each article serves as a mini-review that summarizes work done in recent years. Different viewpoints and methodologies are represented. Dr. Spillmann’s plenary lecture inspiringly describes the creative and collaborative atmosphere in his Freiburg laboratory that brought together many generations of distinguished scientists.

Weaknesses: The different sections of the book do not particularly mesh together and read more like independent pieces. Hence the somewhat cumbersome title, which falls short of communicating the contents of the book.

Recommended Audience: All students of visual sciences, including sensory and cognitive neuroscientists will find this book useful.

Critical Appraisal: This book includes state-of-the-art mini-reviews of a range of visual and multisensory topics, featuring summaries of cutting-edge research from across the field.

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Neuroanatomy Through Clinical Cases

Hal Blumenfeld, MD, PhD.

Scope: This is a neuroanatomy textbook written for medical students in their introductory neuroanatomy course and for students in their clerkship years on a neurology rotation.

The book is divided into 12 chapters. The first 5 chapters deal with the general organization of the nervous system with 1 chapter devoted to neuroradiology. The other chapters describe distinct anatomical entities in the nervous system. Each chapter first describes the general anatomic organization of a specific system followed by clinical vignettes. One entire chapter is devoted to the visual system. It covers the localization of visual complaints and then optic neuritis, branch retinal artery occlusion, hemianopia, migrainous visual loss, and other main conditions.

Strengths: This is an excellent textbook for medical students interested in neurology and for beginning neurology residents. It can also serve as a good reference book on clinical neuroanatomy for ophthalmology residents. Its main strength is the use of clinical cases and scenarios, which bring the study of neuroanatomy to life.
and make it a very practical learning guide for a subject that is often viewed by medical students as dry and irrelevant.

Excellent descriptions of visual fields are given in several clinical cases. Three extensive chapters deal with the brainstem, including several cases of diplopia. Sufficient details are provided to make the cases a valuable learning exercise.

The uniqueness of the book is its inclusion of a variety of clinical vignettes that are written in a problem-based format and that accompany a wide variety of basic neurological complaints encountered by general practitioners. All cases are very clearly written with illustrations accompanying some of them and sufficient references for more detailed learning. Each clinical case emphasizes a specific part of the neurologic examination.

Weaknesses: The text is written in block format. A point format would be easier to digest in many chapters. Most anatomic figures are represented by schematic diagrams and drawings; in some cases photographs would be have been better.

Recommended Audience: Medical students and residents in neurology and ophthalmology will find this book useful.

Critical Appraisal: This is an excellent textbook for anyone teaching neuroanatomy, neurology, or ophthalmology to medical students. Its many clinical vignettes serve as an excellent resource for problem-based learning.

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Case Studies in Stroke: Common and Uncommon Presentations

Michael G. Hennerici, MD, Michael Daffertshofer, MD, Louis R. Caplan, MD, et al.

Scope: This is a multiauthored book encompassing 60 common and uncommon cases related to stroke. Each vignette introduces a short history and salient features of the neurologic examination. Most of the cases include CT, MRI, angiography, transcranial Doppler, or cerebral perfusion scanning. The core of the series lies in the discussion sections. Here, the authors provide a historical perspective and evidence. The reference section at the end of each chapter provides a means to explore the sentinel publications in further detail.

Strengths: The utility of the book stems from its readability and use as an efficient stroll through the usual and unusual manifestations of cerebrovascular disease. Not only does it benefit the novice student or resident physician, but it also serves as a means to expand the differential diagnosis in an interesting way for the most seasoned stroke neurologist. The advanced imaging studies and rich list of historical and current references broaden the appeal. The viewpoints of Drs. Hennerici and Caplan reveal an impressive expertise.

Weaknesses: The neurologic findings in most cases are neglected in favor of intricately described diagnostic studies. Although the random compilation of the cases adds suspense to the page turning, the series lacks organization. As such, its usefulness as a reference guide is probably limited to finding and reviewing one of the chosen pertinent publications cited at the end of each section.

Recommended Audience: Medical students or residents working on an inpatient stroke service, neurologists seeking to expound on the differential diagnosis of stroke, and physicians or other clinical providers seeking an enjoyable read on diagnosis and management of stroke will find this book useful.

Critical Appraisal: The authors remind their readers that the pathologic manifestations of the brain and its vascular supply are far from ordinary and at times can, in fact, be extraordinary.

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The 17th biennial meeting of the International Neuro-Ophthalmology Society (INOS) was held at the Silverado Resort in Napa, California, June 7–12, 2008. Hosted by Anthony Arnold, MD (Los Angeles, CA), John Keltner, MD (Davis, CA), and Neil Miller, MD (Baltimore, MD), the program consisted of 10 sessions that covered virtually every topic in neuro-ophthalmology and featured lectures from 28 invited guests as well as free paper presentations. Two poster sessions consisting of 90 submissions were also part of the program. The meeting was attended by 250 physicians from 18 countries.

The first session concerned disorders of the optic nerve and featured lectures by Solon Thanos (Münster, Germany) discussing new concepts in optic nerve regeneration and repair, John Guy, MD (Miami, FL) discussing his groundbreaking earlier and current work on gene therapy for Leber hereditary optic neuropathy, and Paul Hoffman, MD, PhD (Baltimore, MD) describing the actual and potential effects of electrical stimulation of the optic nerve.

The second session concerned the ocular motor system, beginning with a comprehensive review of the effects of tenotomy on congenital and acquired nystagmus by Lance Optican, PhD (Bethesda, MD), of the National Eye Institute. It was followed by reviews by Christopher Kennard (London, England) of supranuclear disorders of eye movement and by Agnes Wong, MD, PhD (Toronto, ON) of skew deviation and its differentiation from fourth nerve palsy.

The third session dealt with the pupil, including a review of the afferent pupillary pathways by Helmut Wilhelm (Tübingen, Germany), lectures by Randy Kardon, MD, PhD (Iowa City, IA) and Aki Kawasaki, MD (Lausanne, Switzerland) on the nature and significance of melanopsin-containing retinal ganglion cells, and a presentation on the correlation of the state of alertness and the reactivity of the pupil by Barbara Wilhelm (Tübingen, Germany).

The fourth session consisted of several free papers covering a number of areas of neuro-ophthalmology, and the fifth session was devoted to an in-depth discussion of idiopathic intracranial hypertension (IIH), including presentations by Miles Johnston, PhD (Toronto, ON), on the pathways for egress of cerebrospinal fluid, John Pickard (Cambridge, England) on dural venous sinus stenting in patients with IIH, Deborah Friedman, MD (Rochester, NY), on medical therapy for IIH, and Neil Miller, MD, on surgical treatment of IIH. Michael Wall, MD (Iowa City, IA), summed up the information and led a spirited panel discussion.
The sixth session dealt with ocular imaging. John Werner, PhD (Davis, CA), provided an overview of current techniques for imaging of the retina and a glimpse into the not-too-distant future for this field. Helen Danesh-Meyer (Auckland, New Zealand) discussed the use of Heidelberg retinal tomography in neuro-ophthalmology, and Eric Eggenberger, DO (East Lansing, MI) reviewed the optical coherence tomography (OCT) findings in patients enrolled in the Optic Neuritis Treatment Trial.

The seventh session covered eye movements and began with a review by Terry Smith, MD (Los Angeles, CA) on current concepts in the immunology of Graves ophthalmopathy. Mark Kupersmith (New York, NY) discussed medical therapies for ocular myasthenia gravis and their significance for conversion to generalized myasthenia, and Irene Gottlob (Leicester, England) described her breakthrough work on medical therapy for congenital and acquired nystagmus.

The eighth session consisted of a second series of free paper presentations and was followed by a special lecture given by Esriel Killer (Basel, Switzerland) that explored new concepts in the pathogenesis of IIH.

The ninth session was devoted to neuroimaging and featured Philippe Gailloud, MD (Baltimore, MD) discussing the current status of interventional neuroradiology for the treatment of disorders of neuro-ophthalmologic significance and Pablo Villablanca, MD (Los Angeles, CA) comparing the strengths and weaknesses of MRA versus CT angiography for the diagnosis of various cerebrovascular diseases, including acute third cranial nerve palsy.

The tenth and final session was a symposium on multiple sclerosis (MS) and other demyelinating disorders. The speakers for this session included Jeffrey Cohen, MD (Cleveland, OH), who discussed the current and future treatments of MS, Shelley Cross, MD (Rochester, MN) and Jun-ichi Kira (Fukuoka, Japan), who compared MS and neuromyelitis optica and emphasized the clinical findings and the role of the aquaporin-4 antibody in distinguishing between these disorders. The session concluded with a lecture by Laura Balcer, MD (Philadelphia, PA) on the usefulness of low-contrast Sloan letters as well as OCT for outcome assessment in MS clinical trials.

In addition to the scientific program, social activities included a welcome reception, a hotly contested golf
The next INOS meeting will be held in 2010 in Lyon, France. It will be hosted by Alain Vighetto (Lyon, France) and Catherine Tilikete (Lyon, France) with the assistance of Valérie Biousse, MD (Atlanta, GA).

Neil R. Miller, MD
Baltimore, Maryland
From October 24–26, 2008, Tübingen, Germany hosted an international interdisciplinary symposium on the interface between neuro-ophthalmology and low vision.

Subtitled “From Eye to Mind,” it featured three symposia and a demonstration of the latest equipment used to study and enhance untreatable visual impairment. We were shown a video camera hooked to a computer that tracks eye movement strategies in patients with homonymous hemianopia. Researchers use this device to study strategies of seeing with scotomas or hemianopias. We were also introduced to a scanning laser ophthalmoscope adapted for reading analysis.

Eberhardt Zrenner, chair of the Center of Ophthalmology at the University of Tübingen, opened the symposium with praise for hostess Susanne Trauzettel-Klosinski’s work in neuro-ophthalmology and low vision. Dr. Trauzettel-Klosinski credited her mentors Günter Mackensen, Guntram Kommerell, Elfriede Aulhorn (developer of the Tübingen Perimeter), Marco Mumenthaler, Eberhardt Zrenner, William F. Hoyt, MD (San Francisco, CA), and Manfred Mackeben, (San Francisco, CA).

The symposium covered retinal, optic nerve, and chiasmal/retrochiasmal causes of visual impairment. The retinal symposium included presentations on eye movements...
in age-related macular degeneration (AMD) (Gary Rubin, London, England), differences between scanning laser ophthalmoscope (SLO) and MP1 microperimetry in macular disease (Klaus Rohrschneider, Heidelberg, Germany), sensory aspects of seeing after macular translocation surgery (Dorothea Besch, Tübingen), the contribution of low vision aids to reading speed in AMD (Nhung Nguyen, Tübingen), and studies on the preferred retinal locus for reading (Ron Schuchard, Atlanta, GA).

The optic nerve symposium included presentations on pseudotumor cerebri (Kathleen Digre, MD, Salt Lake City, UT), papilledema in brain tumors (Natalia Serova, Moscow, Russia), optic nerve glioma (Helmut Wilhelm, Tübingen), optic nerve meningioma (Klara Landau, Zurich, Switzerland), and optic neuritis (Gordon Plant, London, England).

After lunch we began an exceptional session about cortical adaptation to visual loss, including presentations on the anatomic underpinnings of attention (Hans-Peter Thier, Tübingen), the enhancement of low vision by focal attention (Manfred Mackeben) changes in cortical inhibition after central nervous system damage (Christoph Braun, Trento, Italy), lack of cortical reorganization in macular degeneration (Antony Morland, York, England), the “filling in” phenomenon (Avinoam Safran, Geneva, Switzerland), visual agnosia (Ulrich Schiefer, Tübingen), and visual processing (Lea Hyvarinen, Helsinki, Finland).

We were treated to a birthday party for Dr. Trauzettel-Klosinski at the Bebenhausen Castle. After an excellent lecture on neuro-ophthalmology in art by Pinar Aydin (Ankara, Turkey), we were heartily entertained by MaMiGo-Singers, an excellent a cappella group, two of whose members (Matthias and Michael) are sons of the hostess!

The last day began with a most unusual exhibition of the very first figurines developed 30,000 years ago by Homo sapiens. We returned to the Hoelderlin Tower for a musical concert of lieder and ended a lovely Sunday morning punting down the Neckar River to the poetry of Hoelderlin read in German and English.

Kathleen B. Digre, MD
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Upcoming Meetings

April 17–April 21, 2009
35th American Association of Pediatric Ophthalmology & Strabismus (AAPOS) Annual Meeting
San Francisco, CA
http://www.aapos.org
Contact: aapos@aao.org

April 25–May 2, 2009
Annual Meeting of the American Academy of Neurology (AAN)
Seattle, WA
http://www.aan.com/go/am
Contact: memberservices@aan.com

May 2–May 7, 2009
77th American Association of Neurological Surgeons (AANS) Annual Meeting
San Diego, CA
Contact: info@aans.org

May 3–May 7, 2009
Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting
Ft. Lauderdale, FL
Contact: arvo@arvo.org

May 16–May 19, 2009
Society of Neurological Surgeons Annual Meeting
Salt Lake City, UT
http://www.societytns.org/meeting_info.html
Contact: burchiek@ohsu.edu

May 16–May 21, 2009
47th Annual Meeting of the American Society of Neuroradiology (ASNR)
Vancouver, BC
Contact: meetings@asnr.org

May 26–May 29, 2009
XVIII European Stroke Conference
Stockholm, Sweden
http://www.eurostroke.org/
Contact: hennerici@eurostroke.eu

June 9–June 12, 2009
Canadian Neurological Sciences Federation 44th Annual Congress
Halifax, NS

June 13–June 16, 2009
17th Congress of the European Society of Ophthalmology
Amsterdam, The Netherlands
http://www.soe2009.org/
Contact: soe2009@congrex.com

June 17–June 20, 2009
9th European Neuro-Ophthalmology Society Meeting
Lubeck, Germany
http://www.euros2009.org/
Contact: detlef.koempf@neuro.uni-luebeck.de

June 20–June 24, 2009
19th Meeting of the European Neurological Society
Milan, Italy
http://www.akm.ch/ems2009/
Contact: info@ensinfo.org

June 20–June 23, 2009
Canadian Ophthalmological Society Annual Meeting
Toronto, ON
http://www.eyesite.ca/english/amindex.htm
Contact: cos@eyesite.ca

Sept. 10–Sept. 13, 2009
14th International Headache Congress/51st Annual Scientific Meeting
Philadelphia, PA
http://www.americanheadachesociety.org/
Contact: ahmtgs@talley.com

Sept. 12–Sept. 15, 2009
13th Congress of the European Federation of Neurological Societies (EFNS)
Florence, Italy
http://efns2009.efns.org/
Contact: efns09@kenes.com

Sept. 16–Sept. 18, 2009
32nd Annual Meeting of the Japan Neuroscience Society
Nagoya, Japan
Contact: neuroscience2009@jnss.org

Sept. 25–Sept. 26, 2009
Practical Pearls in Neuro-Ophthalmology: An International Symposium in Honor of Dr. James Sharpe
Toronto, ON
http://events.cmetoronto.ca/website/index/opt0907
Contact: help-OPT0907@cmetoronto.ca

Sept. 30–Oct. 3, 2009
European Association for Vision and Eye Research (EVER) Annual Congress
Portoroz, Slovenia
http://www.ever.be
Contact: ever@ever.be

134th Annual Meeting of the American Neurological Association
Baltimore, MD
http://www.aneuroa.org
Contact: julieratzloff@llmsi.com

Oct. 17–Oct. 21, 2009
39th Annual Meeting of the Society for Neuroscience
Chicago, IL
http://www.sfn.org/index.cfm?pagename=am2009preview
Contact: info@sfn.org

Joint Meeting of the 29th Pan-American Congress of Ophthalmology
113th Annual Meeting of the American Academy of Ophthalmology
San Francisco, CA
http://www.paao.org/congress.html
Contact: info@paao.org

59th Annual Meeting of the Congress of Neurological Surgeons
New Orleans, LA
http://www.neurosurgeon.org/meetings
Contact: info@1cns.org

19th World Congress of Neurology
Bangkok, Thailand
http://www.wcn2009bangkok.com/
Contact: wcn2009@congrex.com

American Society of Neuroimaging 2010 Annual Meeting
San Francisco, CA

http://www.asnweb.org
Contact: asn@llmsi.com

March 6–March 10, 2010
Tucson, AZ
http://www.nanosweb.org/meetings/nanos2009/
Contact: info@nanosweb.org

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

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

July 17–July 22, 2010
International Congress on Neuromuscular Diseases
Naples, Italy
http://www.icnmd2010naples.org/
Contact: ICNMD2010@congrex.com

July 18–July 23, 2010
International Congress on Eye Research (ICER)
Montreal, QC
http://www2.kenes.com/iser2010/pages/home.aspx
Contact: mail@iser.org

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

7th World Stroke Congress
Seoul, Korea
Contact: stroke2010@kenes.com