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Future Directions in Imaging of Neck and Brain Vessels

John Huston, III, MD

Contained in this issue are three articles regarding non-invasive imaging of the neck and brain with computed tomography angiography (CTA) and magnetic resonance angiography (MRA). It is remarkable how important these technology-driven techniques have become in the daily care of our patients.

Technical advances during the past decade have propelled CTA and MRA into a central role in the evaluation and treatment of patients with cervical and cerebrovascular disease. These technological innovations show no sign of slowing. For example, a newly installed 64-slice CT scanner at the Mayo Clinic offers the possibility of isotropic 0.4 × 0.4 × 0.4-mm resolution and time-resolved capabilities. Multi-planar reconstructions of high resolution data sets can produce coronal and sagittal images of the orbits and temporal bones with a single axial acquisition, cutting the typical radiation dose in half. These imagers, which will soon be widely available, can perform CTA from the aortic arch to the circle of Willis in approximately 10 seconds (Paul Lindell, MD, personal communication, August 2004). Coupled with cardiac gating, these exams can demonstrate four-dimensional images (three-dimensional [3D] images displayed at sequential time points), including pulsatility studies of the aortic arch and intracranial aneurysms.

The utility of MRA has increased with the introduction of parallel imaging techniques and the proliferation of clinical 3.0T imaging systems (1). Parallel imaging offers faster image acquisition, higher spatial resolution, or a combination of the two. MR units with a 3.0T magnet have twice the signal compared with standard 1.5T units, which allows improved spectroscopy as well as functional and diffusion tensor imaging. This improving technology will allow MR to move from a technique that makes pictures of anatomy to a technique that quantifies brain physiology.

Although it is easy to become mesmerized by this forward march of technology, it is critical to heed the lessons of the enclosed articles. Tsai et al (2) and Gandhi (3) stress the importance of reviewing source images. Many clinicians rely only on the maximum intensity projection (MIP) images created from the source images. The MIP's ability to make images from multiple directions and present the data in a useful 3D manner results in a user-friendly format. However, the seductive similarity to conventional angiographic representation of the vasculature hides the degradation of image information that occurs during the MIP process. As these authors state, it is essential to review the individual source images to accurately assess for the presence of a dural fistula.

Relying on MIP images alone leads to an overestimation of the degree of carotid stenosis (4). Review of source images is also a critical element for the detection and evaluation of intracranial aneurysms. Vascular irregularities clearly visible on the source images can be less conspicuous or even completely hidden by overlapping vessels on the MIP images. The development of versatile and powerful 3D workstations has made it possible to rapidly review the source and reformatted images. These new and faster workstations can quickly segment or remove tissue elements such as bone and muscle.
Shah et al (5) stress the importance of using multiple sequences to extract the maximum imaging information in the evaluation of cervicocranial arterial dissections. Relying on an individual sequence can lead to an erroneous result or a missed diagnosis. Gandhi (3) points out that this is also true in the identification of dural sinus thrombosis. Correlation of standard T1 and T2 MR imaging, two-dimensional (2D) time-of-flight MRA coronal source images, and contrast-enhanced venography gives clinicians the greatest chance of distinguishing anatomic variants from acute or chronic thrombus within the dural sinuses. This concept is important with imaging of carotid atherosclerotic disease as well (6). Frequently, 2D time-of-flight MRA is used as a scout for a contrast-enhanced MRA. The 2D time-of-flight sequence typically has a signal void when stenosis is 70% or greater. Occasionally, a focal high grade, weblike stenosis cannot be resolved with the contrast-enhanced technique. When a discordance occurs between a signal void on the 2D MRA and no significant stenosis on the contrast-enhanced MRA, it is essential to carefully correlate the results with an ultrasound or proceed to digital subtraction angiography.

Gandhi (3) has presented a widely accepted listing of the appropriate tests for various clinical indications (see his Table 1). However, whether CTA or MRA is performed remains dependent on local expertise, equipment capabilities and availability, and the preferences of the individual practice. It is important to remember that catheter digital subtraction angiography remains the imaging test of final recourse and will identify dural fistulas and dissections not yet resolvable with the best MRA or CTA techniques. However, as the capabilities of MRA and CTA continue to evolve at such a remarkable pace, we need to incorporate the lessons regarding CTA and MRA contained in this issue to provide improved care for our patients.

REFERENCES

Utility of Source Images of Three-Dimensional Time-of-Flight Magnetic Resonance Angiography in the Diagnosis of Indirect Carotid–Cavernous Sinus Fistulas

Yuh-Feng Tsai, MD, Liang-Kong Chen, MD, Cheng-Tau Su, MD, Ta-Nien Lu, MD, Chin-Chu Wu, MD, and Chu-Jen Kuo, MD

Background: We sought to assess the relative contribution of magnetic resonance imaging (MRI), maximum intensity projection (MIP), and source images of three-dimensional (3D) time-of-flight (TOF) magnetic resonance angiography (MRA) to the diagnosis of indirect (dural) carotid–cavernous sinus fistulas (CCFs).

Methods: MRI and 3D TOF MRA were obtained in eight consecutive patients with indirect CCFs confirmed by conventional catheter angiography. Two radiologists masked to the angiographic results reviewed images retrospectively to evaluate the efficacy of MRI and 3D TOF MRA source and MIP images in the diagnosis of CCF.

Results: MRI disclosed CCF in five of eight cases; MIP images of TOF MRA disclosed CCF in four cases; source images of TOF MRA disclosed all eight CCF cases.

Conclusions: The MRA source images are indispensable for a confirmatory diagnosis of indirect (dural) CCF. Underdiagnosis may occur by relying on MRI or 3D TOF MIP images alone.


The gold standard in diagnosis of carotid–cavernous sinus fistula (CCF) is conventional catheter angiography. However, it is an invasive procedure that subjects the patient to the potential risks of procedure-related vascular and radiation injuries, as well as contrast-induced anaphylaxis and renal damage. Moreover, it carries a risk of thromboembolic events as high as 3% in a large series (1). The advent of magnetic resonance angiography (MRA), using blood flow as the physical basis for producing contrast between moving spins and stationary tissue (2), has been applied in the diagnosis of CCF (3,4), but the reported literature is limited. We therefore sought to evaluate the efficacy of MRI, maximal intensity projection (MIP) and source images of three-dimensional (3D) time-of-flight (TOF) MRA in the diagnosis of indirect (dural) CCF.

METHODS

From March 2001 to May 2003, eight consecutive patients (four women and four men; mean age, 64.3 years; range, 43–80 years) with indirect (dural) CCFs were examined with MRI and MRA. The diagnosis was then confirmed by digital subtraction conventional catheter angiography.

MRI and MRA were performed with a 1.5-T unit (Magnetom; Siemens, Symphony, Germany). A standard MRI protocol was performed in all patients and consisted of axial/coronal T1-weighted spin-echo (525/15/90), axial, and/or coronal T2-weighted fast spin-echo (3,500/96 ms), and sagittal fluid attenuated inversion recovery sequences. An intravenous contrast injection was not routinely performed. If so, the protocol consisted of coronal and axial T1-weighted images. Three-dimensional TOF MRA was performed with tilted, optimized, nonsaturating excitation and magnetization transfer techniques. Acquisition parameters of this sequence were fast imaging with steady-state precision 3D; time to recovery, 36 ms; time to echo, 7 ms; flip angle, 25°; matrix, 192 × 512; field of view, 200 mm; three slabs with 32-mm thickness for each slab, 32 partitions of 1-mm thickness. The total acquisition time was 5 minutes 33 seconds. The MRA slabs were axially placed on the skull base by using the sagittal image as reference. All acquisitions included presaturation of venous blood flow. The axial (source) images thus acquired were used for the construction of projection images with a MIP algorithm. For all patients, 12 projections were obtained vertically and horizontally at 15° increments over a 180° range. The MRI, MIP, and source images were filmed for review.
Digital subtraction angiography (DSA) was performed with a 512 × 512 matrix angiographic unit (AngioStar; Siemens). All patients underwent selective catheterization of vertebral, external carotid, and internal carotid arteries with a 4- or 5-French catheter via a femoral artery approach. The DSA images were also filmed for review. The angiographic results were grouped according to the Barrow classification of CCFs (5) as follows: type A, direct high-flow shunt between the internal carotid artery (ICA) and the cavernous sinus (CS); type B, dural shunt between the meningeal branches of ICA and the CS; type C, dural shunt between the meningeal branches of the external carotid artery and the CS; and type D, dural shunt between the CS and the meningeal branches of both the ICA and external carotid artery.

MRI and MRA MIP and source images were reviewed independently by two radiologists who were aware of the clinical history but masked to the catheter angiographic results. MRI, MRA MIP, and MRA source images from the same patient were evaluated on separate dates. The final decision was reached by consensus in cases of discrepancy between the two reviewers.

RESULTS

The efficacy of MRI and MIP and source MRA images in depicting CCF using DSA as the gold standard is illustrated in Table 1. There were seven Barrow type D and one Barrow type B CCFs. MRI alone made the correct diagnosis in five cases; MRA MIP alone made the diagnosis in four cases; and MRA source images alone made the diagnosis in all eight cases by demonstrating flow-related enhancement in the cavernous sinus. In four cases (patients 1, 2, 3, and 8), MRI, MRA MIP, and MRA source images were concordant in making the diagnosis (Figure 1, Patient 8). In five cases (Patients 1, 2, 3, 7, and 8), CCFs were diagnosed by a combination of MRI and MRA MIP, without reviewing the MRA source images. In one case (Patient 1), a type A fistula caused by rupture of an intracavernous aneurysm was diagnosed by MRI and both the MRA MIP and source images, whereas a type D fistula without an associated aneurysm was diagnosed only after DSA (Fig. 2).

DISCUSSION

In this article, we have reported the clinical applications of MRI and MRA to the diagnosis of indirect CCF. In terms of diagnosing CCF, MRI relies on demonstration of abnormal flow voids in the CS and demonstration of complications related to venous hypertension, such as an enlarged CS, engorged draining veins, and swollen extraocular muscles (6–8). Uchino et al (6) reported that they were able to detect MRI flow voids in the CS in 11 of 12 CCFs and a dilated superior ophthalmic vein in 9 of 12 CCFs, and therefore drew the conclusion that MRI would be relatively useful in the diagnosis of indirect CCF. However, we detected MRI flow voids in the CS in only five of eight cases, among which an engorged CS was noted in only four cases, an enlarged cortical draining vein in one case, and swollen extraocular muscles in no cases. Besides, we encountered dilemmas in reviewing MRI flow voids in the CS. First, flow artifacts resulting from pulsation of the cavernous ICA led to signal "smearing" along the phase-encoded direction and corrupted the details of the CS (Fig. 1A). This problem could be eliminated by changing phase-encoded direction, applying a flow compensation technique, or referring to

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Magnetic Resonance Imaging (findings that led to diagnosis)</th>
<th>Magnetic Resonance Angiography</th>
<th>Barrow CCF type*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CCF** (FVCS, SOVE, CVE, CSE)</td>
<td>CCF**</td>
<td>D</td>
</tr>
<tr>
<td>2</td>
<td>CCF (FVCS, CSE)</td>
<td>CCF</td>
<td>D</td>
</tr>
<tr>
<td>3</td>
<td>CCF (FVCS)</td>
<td>CCF</td>
<td>B</td>
</tr>
<tr>
<td>4</td>
<td>Normal</td>
<td>Normal</td>
<td>D</td>
</tr>
<tr>
<td>5</td>
<td>Normal</td>
<td>Normal</td>
<td>D</td>
</tr>
<tr>
<td>6</td>
<td>Normal</td>
<td>Normal</td>
<td>D</td>
</tr>
<tr>
<td>7</td>
<td>CCF (FVCS, SOVE, CSE)</td>
<td>CCF</td>
<td>D</td>
</tr>
<tr>
<td>8</td>
<td>CCF (FVCS, CSE)</td>
<td>CCF</td>
<td>D</td>
</tr>
</tbody>
</table>

* Based on digital subtraction conventional catheter angiography. **In this case, all MRI and MRA images had wrongly suggested a Type A CCF.

FVCS, flow void in cavernous sinus; SOVE, superior ophthalmic vein engorgement; CVE, cavernous sinus enlargement; CVE, cortical vein engorgement.
FIG. 1. Patient 8. Concordance of findings between fast spin-echo magnetic resonance (MRI), three-dimensional time-of-flight magnetic resonance angiography (3D TOF MRA) maximal intensity projection (MIP) and source images in the diagnosis of indirect carotid-cavernous fistula (CCF). Axial T1 (A) and axial T2 (B) MRI at the level of pituitary gland demonstrate flow voids at the medial and posterior aspects of the right cavernous sinus (large arrow). Engorgement of bilateral inferior petrosal sinuses is evident on T1 (small arrows). Flow artifacts resulting from the internal carotid artery are shown on T1 (arrowheads). C. MIP image discloses flow-related enhancement in both cavernous sinuses (arrows). D. The details of abnormal drainage vessels are demonstrated more clearly on MRA source images. In concert with engorgement of bilateral cavernous and inferior petrosal sinuses (large arrows), the imaging of an intercavernous sinus (small arrows), which is slightly corrupted by flow artifacts, is suggestive of a CCF.

FIG. 2. Patient 1. Type D CCF misdiagnosed by MRI and MRA as type A CCF. A. Coronal T1 MRI shows a round, well-defined flow void in the posterior aspect of the right cavernous sinus (arrowheads), which could represent an intracavernous aneurysm. B. MRA source image shows that the signal intensity of the aneurysm-like lesion is inhomogeneous (large arrow), presumably caused by turbulent flow artifact (arrow). There is engorgement of the right inferior petrosal sinus (arrowhead), making the diagnosis of CCF complicating an aneurysmal rupture likely. C. MRA source image at the level of the midbrain discloses engorged cortical draining veins (large and small arrows), further suggesting the diagnosis of CCF. D. Conventional angiography, right ICA injection, shows the cavernous stain of a CCF. There is no evidence of associated aneurysm. E. Conventional angiography, right external carotid artery injection, shows that the fistula also receives blood from the meningeal branches of the internal maxillary artery. The main drainage vessel is a cortical vein (arrowheads). This is therefore a type D CCF.
other images in different planes. On a few occasions, the pulsation of the cerebrospinal fluid resulted in flow voids in the prepontine cistern mimicking enlarged abnormal vessels (Fig. 3). Air in the sphenoid sinus, especially when prominent, led to a diagnostic pitfall because of susceptibility artifacts or partial volume effects at air/CS boundaries (Fig. 3). The cortex of the petrous tip, which lies close to the posterior aspect of CS, also appears as low signal intensity on MRI and was also an obstacle to accurate diagnosis of CCF (Fig. 4). In our experience, reviewing the MRA source images eliminated most of these diagnostic pitfalls.

The most popular and frequently used MRA technique is TOF, which is based on suppressing the signals of background static tissues and selectively imaging the
inflowing spins (blood), a phenomenon called “flow-related enhancement” (2). The original data (the source images), on which blood appears as high signal, can be acquired as a series of overlapping thin sections and reconstructed in a familiar 3D “angiographic” format. Among the techniques used for image reconstruction, the MIP method is the one most frequently used because its implementation is relatively simple and it conveys the densitometric information of the source images without needing to change any parameters (9). In addition, MIP images are easier to interpret than are the source images because the viewer can inspect the angiography-like images in a 3D fashion from several different angles of projection to avoid vessel overlap.

Most clinicians think that MIP images are representative of MRA. This is not true. Information seen on the source images may be lost in the reconstructed MIP images. Thus, reliance on these images alone may lead to misdiagnosis, as occurred in 50% of our cases. Vascular distortion resulting from MIP reconstruction has been well described by Anderson et al (10). For MIP to have a high probability of success, the intensity of the vessel should be on average at least two standard deviations above background intensity on the source images (10,11). Therefore, small or slow-flowing vessels may be poorly visible or even missed on MIP images (9-11). By contrast, MRA source images were able to depict all eight indirect CCFs in our series, although it is well known that blood signal may be lost even on the source images in regions of slow, turbulent, pulsatile, oblique, or in-plane flow (12).

MRA is a collection of all related methods for obtaining angiographic data, not merely the reconstructed 3D angiographic display, but also the original source images. To minimize the diagnostic pitfalls and to achieve the most appropriate diagnosis in CCF, one must have a thorough understanding of the technical limitations of MRA and a careful reviewing of all the images, including MIP and source images.

Despite its ability to diagnose CCF, MRA still cannot compete with DSA in demonstrating the details of feeding and draining vessels. In our series, a case of type D fistula was misinterpreted by MRI and MRA as a type A fistula associated with rupture of an intracavernous aneurysm (Patient 1). An enlarged CS with turbulent flow might explain this shortcoming of MRA (Fig. 2).

REFERENCES

Chronic Myokymia Limited to the Eyelid Is a Benign Condition

Rudrani Banik, MD and Neil R. Miller, MD

Background: Eyelid myokymia, unlike myokymia of the other facial muscles, is assumed to be a benign, self-limited disorder. However, no systematic follow-up study has been performed on patients with chronic, isolated eyelid myokymia to verify its benign nature.

Methods: Retrospective single-institution chart review of 15 patients examined between 1983 and 2002 with a diagnosis of isolated eyelid myokymia who have had at least 12 months of follow-up.

Results: In all patients, symptoms began as unilateral, weekly or biweekly, intermittent eyelid spasms, and progressed to daily spasms over several months. The mean duration of symptoms at first examination was 91 months (range 2.5 months to 20 years). In no patient was the myokymia the first manifestation of a neurologic disease, although one patient progressed to ipsilateral hemifacial spasm. Thirteen patients (86.7%) underwent neuroimaging that gave negative results. The myokymia resolved spontaneously in four patients. Of the remaining 11 patients, eight were treated with botulinum toxin injection at regular intervals, with most reporting an improvement in symptoms.

Conclusion: Chronic isolated eyelid myokymia is a benign condition. It tends not to progress to other facial movement disorders or to be associated with other neurologic disease. It responds well to treatment with botulinum toxin.

Chronic Eyelid Myokymia

JNeuro-Ophthalmol, Vol. 24, No. 4, 2004

This diagnosis were reviewed to identify patients whose myokymia had persisted for at least 3 months on a daily basis. Fifteen patients met this criterion. The charts of these 15 patients were then used to collect data on demographics, symptom duration, associated symptoms, comorbid conditions, clinical signs, neuroimaging studies, treatment, and outcome. An attempt was then made to contact all patients to determine their clinical status. In all 15 cases, follow-up of at least 12 months (range, 12 months to 20 years) after initial assessment in the Neuro-Ophthalmology Unit was available.

RESULTS

Ten patients were female and five were male; all were white. The average age at onset of symptoms was 37.3 years. The right lid was affected in eight cases, the left lid in seven. The lower lid was involved in 14 patients, and the upper lid in one. In all cases, the condition began as episodic twitching of the eyelid lasting several minutes at a time, occurring once or twice weekly. Within 3 to 6 months after onset, the symptoms progressed to daily episodes of spasms lasting several minutes each. The duration of symptoms at the time of initial examination ranged from 2.5 months to 20 years. Seven patients were smokers, eight admitted to moderate alcohol intake, and nine had moderate caffeine intake (Table 1).

Over the course of follow-up, one patient had ipsilateral hemifacial spasm 1 year after the onset of eyelid myokymia symptoms. Another patient had clinically definite multiple sclerosis diagnosed after an episode of cerebellar ataxia followed by optic neuritis. Her myokymia began 4 months before the diagnosis of clinically definite multiple sclerosis and resolved within 6 months. Neuroimaging at that time of onset of the myokymia showed no lesions in the brainstem or along the course of the seventh cranial nerve. The patient subsequently developed chronic progressive multiple sclerosis, but with no recurrence of eyelid myokymia. A third patient with a previous history of transient ischemic attacks characterized by transient diplopia and slurred speech had Alzheimer disease and severe dementia diagnosed 11 years after the onset of myokymia symptoms.

Thirteen (86.7%) of the 15 patients underwent brain neuroimaging. Three had computed tomographic scans and 10 had magnetic resonance imaging scans. In no patient did neuroimaging reveal a mass or other pathologic process affecting the brainstem or the course of the peripheral facial nerve.

The eyelid myokymia resolved spontaneously within 6 months of symptom onset in four patients (in two after the resolution of significant stressors). Among the remaining 11 patients, eight were treated with botulinum toxin (Botox, Allergan, Inc., Irvine, CA) injection into the affected eyelid.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at onset/gender</th>
<th>Symptom duration at presentation (months)</th>
<th>Progression</th>
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<th>Neuroimaging</th>
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<tr>
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<td>36/M</td>
<td>36</td>
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<td>No</td>
<td>MRI normal</td>
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<tr>
<td>2</td>
<td>35/F</td>
<td>30</td>
<td>Yes, to ipsilateral hemifacial spasm</td>
<td>No</td>
<td>MRI (&gt;2) normal</td>
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<tr>
<td>3</td>
<td>45/F</td>
<td>10</td>
<td>No</td>
<td>No</td>
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<tr>
<td>4</td>
<td>47/F</td>
<td>8</td>
<td>No</td>
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<td>10</td>
<td>36/F</td>
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<td>11</td>
<td>57/F</td>
<td>2.5</td>
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<td>30/M</td>
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<td>24</td>
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<td>MRI normal</td>
</tr>
</tbody>
</table>

Legend: MRI = Magnetic resonance imaging; MRA = magnetic resonance angiography; CT = computed tomography.
Two of these patients had resolution of the myokymia after a single injection, five patients required repeat annual or biannual treatments, and one patient had no improvement in myokymia after an initial botulinum toxin injection and did not return for subsequent treatment.

**DISCUSSION**

Isolated eyelid myokymia, usually affecting the lower lid, tends to be a transient unilateral condition. However, in some cases, the condition becomes chronic. Although previous reports have suggested that chronic eyelid myokymia can progress to involve the lower face and that myokymia involving the lower face is often a manifestation of a more serious underlying condition affecting the caudal brainstem (3,6–8), our experience with persistent myokymia limited to the eyelid suggests that it is benign. Among our 15 patients, 12 (80%) had no evidence of any underlying neurologic disorder during a follow-up period that ranged from 12 to 240 months, with a mean of 91 months. Of the three patients who did have other findings, only one had a related condition, ipsilateral hemifacial spasm. In the patient in whom clinically definite multiple sclerosis developed, there was no definite evidence by neuromaging that the eyelid myokymia was related, nor did the myokymia symptoms lead to the diagnosis. One patient had Alzheimer disease but there was no temporal association with her eyelid myokymia.

Thus, although patients with isolated, persistent eyelid myokymia routinely undergo neuromaging studies to rule out an intrinsic or extrinsic process affecting the pons, the performance of such studies is unwarranted because of its very low yield.

In facial myokymia, these imaging studies are undertaken to discover lesions that may be supranuclear, perinuclear, nuclear, or infranuclear. In some cases, there is a lesion in the brainstem rostral to the facial nerve nucleus leading to supranuclear disinhibition (8). In other cases, loss of perinuclear interneurons synapsing on the facial nerve nucleus results in functional deafferentation (8). Still other cases are caused by damage to peripheral nerve fibers, as after radiation therapy, in which there is segmental demyelination of peripheral nerve fibers innervating the orbicularis oculi (as evidenced by transcranial magnetic stimulation studies) (9) or in which antibodies to voltage-gated potassium channels (10) are present. Eaptic transmission with 'cross-talk' of fibers or ectopic excitation may occur in neighboring branches of the facial nerve. The result is hyperexcitability of facial nerve fibers.

The cause of chronic, isolated eyelid myokymia is less clear. The chronic, localized nature of the process without progression to involve other ipsilateral facial muscle groups suggests the lesion is peripheral. However, no electromyographic studies have yet been performed on this particular subset of patients. Psychosocial factors, such as fatigue, lack of sleep, physical exertion, stress, smoking, alcohol, or caffeine may play a role in the development and persistence of the process. More than half of our patients admitted to one or more of the latter three habits, but in no case could we establish a temporal relationship between the onset of symptoms and these habits. It is noteworthy that in two cases, the myokymia did improve within 6 months after relief of work-related stress and anxiety.

We believe that most patients with isolated eyelid myokymia should be managed conservatively, with reassurance, rest, and elimination of or reduction in possible risk factors, such as smoking, alcohol ingestion, and caffeine intake. If the myokymia persists for more than 3 months and is bothersome to the patient, further intervention may be warranted. Although limited surgical myectomy of the affected pretarsal and preseptal orbicularis oculi has been shown to be of benefit and, in some cases, curative (5), palliative injections of botulinum toxin are also quite successful and less invasive than surgery (11). Interestingly, two of our patients had complete resolution of their myokymia with a single injection, as has been reported previously in cases of eyelid and facial myokymia (5,11,12). Whether this outcome was a direct consequence of the treatment, or simply coincident with the natural history of the condition, is impossible to determine.

**REFERENCES**


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Optic Nerve Calcification After Trauma

John L. Crompton, FRANZCO, FRACS, Justin O’Day, FRANZCO, FRACS, FRACP, and Ahmed Hassan, MBBS

FIG. 1. Case 1. Sagittal (A), coronal (B), and axial (C) computed tomography scans show focal high signal within the left optic nerve. Coronal T2-weighted (D) and axial T1-weighted (E) magnetic resonance imaging scans show low signal within the left intraorbital optic nerve consistent with calcium.

Abstract: Two patients with remote histories of severe optic nerve trauma displayed profound intraorbital optic nerve calcification on imaging studies. The presumed mechanism is optic nerve hemorrhage. Although calcification is known to occur long after brain hemorrhage, no comparable cases have been previously reported.

CASE 1

A 43-year-old restaurant manager was referred for a neuro-ophthalmology opinion in Adelaide in 2001. He had consulted a neurologist for neck pain, at which time computed tomography and magnetic resonance imaging scanning showed a well-circumscribed calcified lesion within the left optic nerve (Fig. 1). The signal void in the coronal view localized the lesion to the center of the optic nerve.

The patient gave a history of having been accidentally hit in the left eye by a baseball at age 7 in New York. The impact was severe, causing loss of consciousness. No medical records were available.

On our examination, his corrected visual acuity was 20/20, but there was a left relative afferent pupil. Ishihara color vision testing was normal OD; one error was made OS. A relatively diminished light intensity of only 60% was reported OS. Computerized visual fields showed inferior patchy loss consistent with an inferior arcuate scotoma, along with an enlarged blind spot. The optic disc OD appeared normal, but the optic disc OS showed diffuse pallor.
There were no ocular adnexal abnormalities, proptosis, or limitations of eye movements. Ocular alignment was normal.

CASE 2

An 84-year-old man described having very poor vision OD since being involved in a motorcycle accident 50 years earlier, in which he recalled sustaining a right orbital injury.

On our examination, corrected visual acuity was hand movements OD and 20/30 OS. A relative afferent pupil defect was present OD. There was gross constriction of the visual field OD and a normal visual field OS. The optic disc OD was pale, whereas the optic disc OS was normal. There were no ocular adnexal or eye movement abnormalities.

Computed tomography demonstrated heavy calcification within the right optic nerve confined to the orbit (Fig. 2).

DISCUSSION

The striking optic nerve calcification in both cases is likely to reflect a secondary phenomenon after traumatic injury with hemorrhage. There are many reports of calcification in the brain and spinal cord after traumatic hemorrhage (1). Approximately 10% of patients who have sustained intracerebral hemorrhage demonstrated calcified lesions on follow-up radiologic studies in one report (2).

The main differential diagnosis is calcification within an optic nerve sheath meningioma (3,4). However, calcification in a meningioma is typically a tubular thickening involving the perimeter of the nerve, whereas in our cases, the full thickness of the nerve was calcified. Furthermore, the visual acuity and field defects in both cases had remained stationary for many years, which would be atypical for meningioma. Idiopathic calcification of the dura and optic nerves has been reported (5,6), but perhaps such idiopathic cases represent missed trauma or meningioma (7).

REFERENCES

Magnetic Resonance Imaging of Choroidal Inflammation in Vogt-Koyanagi-Harada Disease

Michael S. Vaphiades, DO and Russell W. Read, MD

Abstract: Acute binocular visual loss, photophobia, headache, and pulsatile tinnitus developed in a 51-year-old woman. Ophthalmologic examination showed bilateral optic disc edema with peripapillary nerve fiber layer hemorrhages. Lumbar puncture disclosed a monocytic pleocytosis. A diagnosis of Vogt-Koyanagi-Harada disease was made. Magnetic resonance imaging showed striking enhancement and thickening of the posterior ocular wall. A macular star figure appeared several days after prednisone treatment was begun. Laboratory evaluation was entirely negative. Within weeks, the clinical manifestations had resolved except for retinal striae. This is the third report of the magnetic resonance imaging visualization of choroidal inflammation in Vogt-Koyanagi-Harada disease and shows the imaging abnormalities in finer detail than earlier reports.


A 51-year-old woman presented with a 6-week history of bilateral visual loss accompanied by photophobia, severe headaches, and pulsatile tinnitus.

Blood pressure was normal. Best-corrected visual acuities were 20/400 OD and 20/70 OS. Automated perimetry showed nonspecifically constricted visual fields OU. Pupils were equal in size and reacted briskly to direct light without a relative afferent pupillary defect. Ocular motility, trigeminal and facial nerve function, palpebral fissures, and exophthalmometry were normal. Slit-lamp biomicroscopy revealed normal anterior segments bilaterally. Tonometry was normal OU. Dilated fundus examination showed swollen optic nerves OU and low-lying serous...
retinal detachments OU. There were peripapillary nerve fiber layer hemorrhages OD.

Cranial and orbital magnetic resonance imaging (MRI) showed diffuse bilateral enhancement of the posterior ocular wall and serous retinal detachment OS (Fig. 1). Ultrasonography revealed diffuse choroidal thickening without evidence of scleritis. A lumbar puncture showed a normal opening pressure with a leukocyte count of 57/mm³ (100% monocytes), no red cells, normal protein, glucose, cryptococcal antigen, and luetic titers.

A diagnosis of Vogt-Koyanagi-Harada (VKH) disease was made and the patient was treated with prednisone 60 mg/d. The patient experienced relief of her headache. Seven days after institution of oral prednisone, the exudative detachments were decreased in size and macular exudates appeared as a partial macular star figure. (Fig. 2). Fluorescein angiography at this time showed continued disc hyperemia and peripapillary leakage. Laboratory evaluation for causes of Leber stellate neuroretinitis was negative, including serologies for syphilis, Bartonella henselae and Bartonella quintana, Borrelia burgdorferi, Ehrlichia species, and luetic titers.

Over the course of 10 weeks, the patient’s visual acuity improved to 20/20 OU, with complete resolution of the serous retinal detachments and macular exudates. Macular striae persist, but the patient has no metamorphopsia.

VKH disease consists of bilateral diffuse choroiditis with exudative retinal detachments and papillitis (1). A macular star figure has apparently not been previously reported in this condition. Auditory and central nervous system involvement in VKH disease usually precedes ocular findings and is typified by hearing loss, tinnitus, and meningismus with associated cerebrospinal fluid pleocytosis. Involvement of the integumentary system occurs later in the disease course and may include alopecia, poliosis, or vitiligo (1,2).

The posterior ocular wall inflammation consists of choroiditis without scleritis (2). This manifestation was first imaged in 1990 (3) with a sagittal MRI using a surface coil. The scan showed choroidal thickening, a finding that was also appreciated on CT (3). In 1994, Ibanez et al (4) demonstrated intense enhancement and thickening of the choroid on axial T1-weighted orbital MRI. Our case illustrates these findings in even higher resolution.

REFERENCES
Progression from Anomalous Optic Discs to Visible Optic Disc Drusen

Terrence S. Spencer, MD, Bradley J. Katz, MD, PhD, Steve W. Weber, MD, and Kathleen B. Digre, MD

Abstract: At age 5, a patient underwent fundus photography that disclosed elevated optic discs without drusen. A head computed tomography did not show optic nerve calcification. At age 9, no disc drusen were evident by ophthalmoscopy, but a CT now showed optic nerve calcification. At age 12, optic disc drusen were faintly evident on photographs; visual fields showed blind spot enlargement OD and an arcuate defect OS. At age 21, he had numerous discrete disc drusen in both eyes, disc pallor, and slight progression of the visual field defects. This case documents the progression from anomalous optic discs to ophthalmoscopically visible optic nerve drusen over a 16-year period.

(J Neuro-Ophthalmol 2004;24: 297-298)

At age 2, an otherwise healthy boy underwent medial rectus recession OU for congenital esotropia. Fundus examinations were recorded as normal. On routine follow-up at age 5, he was found to have markedly elevated optic discs (Fig. 1). No drusen were observed. Computed tomography of the head did not show calcification associated with buried optic nerve drusen.

Over the next several years, he and immediate family members underwent additional ophthalmologic examinations that disclosed no disc anomalies in any family members. At age 9, drusen were still not ophthalmoscopically visible, but computed tomography now revealed optic nerve calcification. He was presumed to have buried optic nerve drusen (OND). At age 10, automated perimetry revealed an enlarged blind spot OD and arcuate defects OS.

(Age 5: both discs show ophthalmoscopic elevation but no drusen. A head computed tomography showed no optic nerve calcification. Age 12: the right optic disc has not changed ophthalmoscopically, but the left disc now has a "lumpy bumpy" appearance and appears pale. Three years earlier, computed tomography had shown optic disc calcification in both eyes. Age 21: multiple large drusen are now ophthalmoscopically visible bilaterally.

(Fig. 2). At age 12, fundus photos showed a stable appearance of the right optic nerve, but the left optic nerve had taken on a "lumpy bumpy" appearance with some pallor (Fig. 1).
FIG. 2. Minimal progression of visual field defects from age 10 to age 21. A. Age 10: there is an enlarged blind spot OD and superior and inferior arcuate defects OS. B. Age 21: the defects OS have changed minimally and very shallow arcuate defects have appeared OD.

At age 21, he still had no visual symptoms but now manifested ophthalmoscopically obvious optic disc drusen bilaterally (Fig. 1). Perimetry disclosed minimal progression of the visual field defects (Fig. 2). Although he did not have ocular hypertension, he was treated with topical brimonidine 0.2% in an effort to stabilize his visual field defects.

OND are calcified, acellular, laminated concretions that form within the substance of the optic nerve. They occur in approximately 2% of the population (1) and are transmitted as an autosomal dominant trait (2). Some cases of OND appear to be sporadic (3), but most investigators agree that OND is a genetic disease that segregates in an autosomal dominant fashion (4), suggesting that OND is the most common inherited optic neuropathy.

Some drusen are visible on funduscopic examination (“visible drusen”), whereas some optic nerves harbor drusen that are not visible on ophthalmoscopy (“buried drusen”). Buried drusen may be detected by ultrasonography (5), computed tomography (6), or red-free photography (7). Although most OND patients are asymptomatic, 71% to 75% have peripheral visual defects (8). There is no known treatment of the visual field loss associated with OND.

This case demonstrates how anomalously elevated optic nerves in a child can represent buried optic disc drusen (9,10), which may eventually evolve to visible OND.

REFERENCES
Cervicocranial Arterial Dissections

Louis R. Caplan MD and Valérie Biousse, MD

Abstract: Cervicocranial dissections are an increasingly recognized cause of stroke in the young. When the dissections narrow the vascular lumen, they often alter blood flow enough to cause transient ischemic attacks in the brain. Alterations in the endothelium activate the coagulation cascade, leading to the formation of intramural clot that may embolize distally to cause brain infarction. Pain and neuro-ophthalmic symptoms and signs are common manifestations.

(JNeuro-Ophthalmol 2004;24: 299–305)

PATHOGENESIS OF CERVICOCRANIAL DISSECTIONS

Dissections are tears in arteries, almost always involving the medial coat (1–10). They may be traumatic or "spontaneous" in origin. In fact, the majority of dissections probably involve some trauma or mechanical stress, with sudden neck movements and stretching often implicated. Some inciting events may be trivial, such as lunging for a tennis ball or sudden turning of the neck while driving a car. Many such events are forgotten or considered too inconsequential to be mentioned by the patient (5). Congenital and acquired abnormalities of the arterial media and elastic tissue can render patients more vulnerable to dissection (5,7,11,12). Inherited disorders of connective tissue (Marfan syndrome, Ehlers-Danlos syndrome, pseudoxanthoma elasticum), cystic medial necrosis, and fibromuscular dysplasia predispose to dissection (5,11,12). Ultrastructural connective tissue abnormalities of collagen and extracellular matrix are sometimes found in the skin of patients with extracranial arterial dissections (11,12). In addition, indirect evidence of a generalized arteriopathy is suggested by the association of spontaneous dissections with intracranial pseudoaneurysms, a widened aortic root, arterial redundancies, and increased arterial distensibility (5,7,12,13). Migraine is more common in patients with dissection (14), and a recent history of upper respiratory tract infection has also been shown to be a risk factor for cervicocranial dissections (15).

Dissections often involve loops and redundant portions of the extracranial arteries (Fig. 1) (16). They probably begin with a tear in the media, which leads to bleeding within the arterial wall. Intramural blood then dissects longitudinally, spreading along the vessel proximally or distally (Fig. 2). The dissection can tear through the intima, allowing the partially coagulated intramural blood to enter the arterial lumen. The arterial wall, expanded by intramural blood, can also compress the lumen. Some dissections begin at the intimal surface and dissect into the media. Intimal flaps are then often present. At times, the major dissection plane is between the media and the adventitia, causing an aneurysmal outpouching of the arterial wall (Fig. 1) (5,7,9,17–27).

Extracranial dissections cause symptoms primarily by the presence of luminal compromise and luminal clot. Dissections through the adventitia may rupture into the surrounding neck muscles and fascia with formation of a pseudoaneurysm. They may compromise blood flow. Partially clotted blood in the media may rupture into the lumen. Irritation of the endothelium causes release of endothelins, which activate platelets and the coagulation cascade, contributing to formation of intraluminal thrombus. The luminal clot is usually loosely adherent to the intima and can readily embolize distally. In the weeks after dissection, the intramural blood is absorbed and the lumen usually returns to its normal size. Aneurysmal pouches may remain as a mark of the healed lesion. Acute luminal compromise or occlusion (Fig. 3) may cause hypoperfusion and brain ischemia, although infarction is more often caused by embolization or propagation of luminal thrombus (1,2,19).

SITES OF CERVICOCRANIAL DISSECTIONS

Dissections usually involve mobile portions of arteries. They do not occur at the fixed origins of the carotid and vertebral arteries from the common carotid and subclavian arteries, respectively. The extracranial internal carotid artery (ICA), the most commonly affected artery, is fixed at its origin and at its dural penetration, making the cervical portion the most mobile and vulnerable to dissections (Fig.
FIG. 1. Conventional angiogram showing a spontaneous internal carotid artery (ICA) dissection involving a complete loop (coil) in the distal portion of the ICA. The dissected artery is irregular below the loop. There is a pseudoaneurysm within the loop (arrow).

2) (1,3,4,7,17-25). The upper cervical segment is an unusual site for atherosclerosis, which almost invariably affects the ICA origin or the carotid siphon. Emboli arising from nuchal ICA dissections most often go into middle cerebral artery (MCA) branches.

The extracranial vertebral arteries (ECVAs) are relatively fixed at their origins from the subclavian arteries, in their intraosseous portion (V₂), and by the dura at the point of intracranial penetration. The short, moveable portions between these segments are vulnerable to tearing, stretching, and dissection. Therefore, dissections tend to involve the proximal (V₁) portion of the ECVAs well above its origin from the subclavian artery or the distal (V₃) segment. In some cases, all segments of the vessel are dissected (Fig. 4). V₁ dissections are almost always unilateral. The distal extracranial portion (V₃) is the most common location for dissection within the posterior circulation (2,19,22,27). Distal (V₃) ECVAs dissections often extend into the intracranial vertebral artery (ICVA) and occasionally caudally into the intraosseous (V₂) segment. Distal ECVAs dissections are often bilateral, even though pain and other symptoms may be unilateral.

Emboli from ECVAs dissections most often go to the ICVs, causing posterior inferior cerebellar artery territory cerebellar or lateral medullary ischemia and infarction. Less often emboli reach the distal basilar, superior cerebellar, or posterior cerebral arteries (2,7,19).

Intracranial vascular dissections are less common than extracranial dissections. They can cause infarction,
CLINICAL MANIFESTATIONS OF CERVICO CRANIAL DISSECTIONS

Internal Carotid Artery Dissections

In patients with ICA neck dissections, pain is often the most impressive feature (Table 1) (1,3,4,7,17-31). Ipsilateral throbbing headache and sharp pain in the neck, jaw, pharynx, or face separate dissection from the ordinarily painless atherosclerotic occlusion. After being present for several days, pain may disappear, only to recur days or even weeks later, and may be accompanied by ischemic attacks or strokes. The sympathetic nerve fibers traveling along the wall of the ICA are usually disturbed, leading to an ipsilateral partial Horner syndrome, characterized by ptosis and miosis. Facial sweat function is preserved because the sympathetic innervation of the sweat glands travels along the external carotid artery.

In internal carotid artery dissection, transient ischemic attacks are common and may involve the ipsilateral eye and brain. The spells often come more frequently than in atherosclerotic carotid stenosis, which led C. Miller Fisher, MD, to coin the term “carotid allegro” (3,4). Some patients with ICA dissection have visual scintillations and bright sparkles resembling migraine, even though many have had subarachnoid bleeding, or mass effects (2,19,26,27). When arteries dissect between the media and the intima, luminal narrowing and local hypoperfusion usually occur and lead to infarction in the regions of supply. In the anterior circulation, the supraclinoid ICA and mainstem MCA are most often involved. In the posterior circulation, the ICVAs and the basilar artery are most often affected (Fig. 5). When dissections extend between the media and the adventitia, pseudoaneurysms and tears through the adventitia may lead to subarachnoid hemorrhage, which can be recurrent. At times, dissections lead to prominent aneurysmal masses, which can present as space-taking lesions that compress adjacent cranial nerves or brain parenchyma (Fig. 5).
TABLE 1. Clinical features in 635 patients with extracranial carotid artery dissections**

<table>
<thead>
<tr>
<th>Gender</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>53%</td>
<td>47%</td>
</tr>
<tr>
<td>Laterality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>86%</td>
<td></td>
</tr>
<tr>
<td>Bilateral</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>Major presenting event*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain infarction</td>
<td>46%</td>
<td></td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Neck or head pain</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>Pulsatile tinnitus only</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Associated features at diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head or neck pain</td>
<td>67%</td>
<td></td>
</tr>
<tr>
<td>Tinnitus or bruit</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Horner syndrome</td>
<td>32%</td>
<td></td>
</tr>
<tr>
<td>Lingual paresis</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Clinical outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No neurologic sequelae</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>Mild deficit</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>Moderate to severe deficit</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>4%</td>
<td></td>
</tr>
</tbody>
</table>

* Major presenting complaint leading to evaluation, not necessarily the initial symptom.

no personal or family history of migraine. Some patients hear a pulsatile noise in the head or ear. Transient ischemic attacks are probably caused by luminal compromise, with distal hypoperfusion, but most patients with severe strokes have evidence of embolization of clot to the MCA from thrombus at the site of the dissection. When the ICA dissection extends to the carotid siphon, ischemic optic neuropathy can develop as a result of decreased perfusion of arteries supplying the optic nerve. Stroke may occur soon after the ICA dissection or days to weeks later. Very late stroke is rare. At times, clinical manifestations of dissection may occur in steps as an initial tear extends and more intramuscular bleeding develops. Both carotid arteries and even the ECVs may become dissected at the same time.

If pseudoaneurysm formation results from ICA dissection, dysfunction of the lower cranial nerves at the skull base may develop in the patient. Dysgeusia, weakness, and atrophy of the tongue are the most common cranial nerve signs. The lingual weakness and atrophy are caused by compression of the hypoglossal (XII) nerve as it lies adjacent to the carotid sheath. At times, cranial nerves IX, X, XI, and XII are involved together. Intracranial ICA dissections are characterized by headache, together with signs of hemispheric MCA territory infarction.

Vertebral Artery Dissections

Extracranial vertebral artery dissections were first recognized in patients who had sustained neck trauma or had undergone chiropractic manipulation, but ECVA injuries have also been reported in patients who manipulate their own necks, who maintain their necks in a fixed position for some time, or who make sudden abrupt neck movements. ECVA dissections also occur after surgery and resuscitation. These lesions most often involve the distal ECVA (V3). Spontaneous ECVA dissections closely mimic those related to trauma.

Pain in the posterior neck or mastoid region often precedes neurologic symptoms by hours, days, and weeks, and may be the only manifestation. Transient ischemic attacks, less common than in ICA dissections, are

TABLE 2. Clinical features in 174 patients with extracranial vertebral artery dissections**

<table>
<thead>
<tr>
<th>Gender</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>43%</td>
<td>57%</td>
</tr>
<tr>
<td>Laterality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>69%</td>
<td></td>
</tr>
<tr>
<td>Bilateral</td>
<td>31%</td>
<td></td>
</tr>
<tr>
<td>Major presenting event*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain infarction</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>At onset</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>After onset</td>
<td>83%</td>
<td></td>
</tr>
<tr>
<td>&quot;Lateral medullary&quot; symptoms</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>Neck or head pain</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>Clinical outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No or mild neurologic deficit</td>
<td>83%</td>
<td></td>
</tr>
<tr>
<td>Mild deficit</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>Moderate or severe deficit</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>6%</td>
<td></td>
</tr>
</tbody>
</table>

* Major presenting complaint leading to evaluation, not necessarily the initial symptom.

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manifested by dizziness, diplopia, veering, staggering, and dysarthria. Infarcts are explained by embolization of fresh thrombus to the ICVA (9,19). Occasionally, dissections extend or begin intracranially. They usually occur in the posterior inferior cerebellar artery domain, affecting the cerebellum and often the dorsolateral medulla. Sometimes emboli reach the superior cerebellar arteries, the main basilar artery, or the posterior cerebral arteries. Aneurysmal dilatation of the ECVA adjacent to nerve roots may cause radicular pain and can lead to radicular motor, sensory, and reflex abnormalities (46,47). Occasionally, spinal cord infarction results because of hypoperfusion in the branches of the ECVA that supply the cervical spinal cord (48).

ICVA dissections usually extend into the basilar artery, causing brainstem infarction (2,7,18,19). Subarachnoid hemorrhage is another important presentation of ICVA dissection (2,9,10,19,26,27). Occasionally, dissections develop in the basilar artery and rarely in the posterior cerebral arteries. In the past, intracranial dissections were considered neurologically devastating or fatal, but modern technology has led to increased recognition that patients with intracranial dissections may have only minor signs.

Neuro-ophthalmic manifestations of carotid and vertebral dissections are common (Tables 1–3). In carotid dissections, Horner syndrome is a presenting manifestation in up to 80% of cases evaluated by a neuro-ophthalmologist (Table 3). The second most common symptom is ipsilateral transient monocular visual loss, estimated to a presenting symptom in 61% of cases (Table 3). In vertebral dissections, persistent manifestations of lateral medullary dysfunction (Horner syndrome, nystagmus, skew deviation, ocular lateropulsion, or ipsilateral first division trigeminal sensory loss) are found in more than 50% of cases (Table 2).

**TABLE 3. Neuro-ophthalmic manifestations in 146 patients with carotid artery dissections***

<table>
<thead>
<tr>
<th>Neuro-ophthalmic Manifestations</th>
<th>Frequency as Overall Frequency</th>
<th>Presenting Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuro-ophthalmic manifestations</td>
<td>62.5%</td>
<td>52%</td>
</tr>
<tr>
<td>Painful Horner syndrome</td>
<td>44.5%</td>
<td>80%</td>
</tr>
<tr>
<td>Transient monocular visual loss</td>
<td>28%**</td>
<td>61%</td>
</tr>
<tr>
<td>Ischemic optic neuropathy</td>
<td>2.5%</td>
<td>0%</td>
</tr>
<tr>
<td>Central retinal artery occlusion</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Ischemic ocular syndrome</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Ocular motor nerve palsy</td>
<td>&lt;1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

* Isolated in 49% with TIA or stroke in 51%.
** Associated with pain in 75.5%; with Horner syndrome in 31.5%.

**FIG. 6.** Color Doppler study showing an internal carotid artery dissection. The dissected artery is enlarged secondary to the hematoma within the arterial wall (white arrow). The lumen is reduced (arrow).

**INVESTIGATION OF PATIENTS WITH SUSPECTED CERVICOCRANIAL DISSECTION**

The diagnosis of cervicocranal dissection can be made noninvasively with ultrasound, computed tomography, or magnetic resonance imaging (MRI)/magnetic resonance angiography (MRA) or with catheter angiography. Whereas catheter angiography was formerly considered the gold standard, noninvasive methods are now so accurate that they suffice (7,19,49–53).

B-mode ultrasound can show tapering of the ICA lumen, beginning well above the ICA origin, an irregular membrane crossing the lumen, or actual demonstration of true and false lumens (Fig. 6) (49–51). Doppler can show a typical pattern characterized by a high-amplitude signal with markedly reduced systolic Doppler frequencies and alternating flow directions over the region of luminal narrowing (50,51). This Doppler signal probably results from abnormal vessel wall pulsations and some bidirectional movement of the blood column. Duplex scans of the ECVAs can also suggest dissection (49,51). Typical findings are increased arterial diameter, decreased pulsatility, intravascular abnormal echoes, and hemodynamic evidence of decreased flow. Color Doppler flow imaging can also show the regions of dissection within the neck. Diminished flow in the high neck at the level of the atlas detected by transcranial Doppler suggest the presence of distal
ECVA dissections. In patients with extracranial ICA dissections, transcranial Doppler may show diminished intracranial velocities in the ICA siphon and the MCA. When this occurs in young patients without risk factors for atherosclerosis or embolism who have normal ICA bifurcations in the neck, the diagnosis of dissection is likely.

Computed tomography and MRI, taken as axial cross-sections through the area of dissection, have shown the intramural bleeding and mural expansion (Fig. 7). MRA and computed tomographic angiography can also show dissections (52,53).

The most common catheter angiographic finding is a string sign, consisting of a long, narrow column of contrast material that begins distal to the carotid bifurcation and often extending to the base of the skull (Figs. 2 and 3) (3,4). There may also be total occlusion of the ICA. This occlusion differs from the typical atherosclerotic occlusion, beginning more than 2 cm distal to the origin of the ICA, sparing the siphon, and having a gradually tapering segment that ends in the occlusion. There may also be localized aneurysmal sacs or outpouchings, both proximal and distal, along a narrowed, a normal, or an unusually dilated portion of the artery.

**REFERENCES**

Computed Tomography and Magnetic Resonance Angiography in Cervicocranial Vascular Disease

Dheeraj Gandhi, MD

Abstract: Although catheter angiography, or digital subtraction angiography (DSA), is still regarded as the gold standard for imaging of cervicocranial vascular disease, its morbidity, cost, and time-consuming features have prompted the development of noninvasive techniques based on computed tomography (CT) and magnetic resonance imaging. With the advent of powerful software, CT and magnetic resonance angiography are complementing and, in some cases, even replacing DSA in the diagnostic evaluation of carotid atherostenosis, unruptured aneurysms, dissections, stroke, penetrating trauma to the neck, and dural venous sinus occlusive disease. They offer advantages over DSA not only in reduced morbidity and time-saving but also in assessment of brain parenchyma, quantitative perfusion, and abnormalities of vessel walls. In the evaluation of blunt neck injuries and intracranial vascular malformations, fistulas, and vasculitis, CT and magnetic resonance angiography still do not provide as much information as DSA.


Cerebral catheter angiography, or digital subtraction angiography (DSA), is still generally regarded as the gold standard for the imaging of cerebrovascular disorders. But despite technical advances (digital imaging systems, smaller catheters, hydrophilic guide wires, and safer contrast media), it remains a time-consuming examination with a small but significant (0.5%) rate of permanent neurologic complications (1,2). This has prompted considerable interest in the development of alternative non-invasive techniques.

Cross-sectional techniques like computed tomography (CT) and magnetic resonance imaging (MRI) offer not only reduced morbidity and time-saving but also the possibility of combined assessment of brain parenchyma and its vascular supply including, most recently, quantitative assessment of perfusion. These techniques also provide important information about vessel walls, enabling early detection and characterization of lesions before alterations in the vessel lumen occur. Three-dimensional reconstructions of volume data from CT angiography (CTA) and magnetic resonance angiography (MRA) excellently depict the spatial relationship of complex vascular lesions to the surrounding structures, providing valuable information for the surgeon. CTA and MRA are also quicker to perform and require fewer resources in terms of staffing and equipment. Most such examinations (especially CTA) can be performed without sedation.

With continued advances in hardware and software, CTA and MRA are slowly but surely replacing DSA for many diagnostic questions. In the future, DSA will likely be reserved largely for interventional procedures.

COMPUTED TOMOGRAPHY ANGIOGRAPHY

CTA is a rapid, non-invasive imaging technique that can produce quality angiographic projections of the cervical and cerebral vasculature after intravenous injection of radiographic contrast media. Although it has been in use since the early 1980s (3), interest in CTA has been rekindled with the advent of helical and multislice CT scanners. These modern scanners allow acquisition of extremely high-resolution images of extracranial and intracranial vasculature within 1 minute or less (3). Using commercially available software, one can generate two-dimensional (2D) and three-dimensional (3D) images of vessels from the raw data. These reconstructed images can be viewed from any angle and with varied window settings. Shaded surface displays and maximum intensity projection (MIP) are the most popular algorithms. It is also possible to view the inner surface of the vessel wall and navigate along the vessel lumen (intra-arterial endoscopy) (3).

Intracranial Aneurysms

CTA has been widely used in the detection and characterization of intracranial aneurysms. It has replaced DSA as a primary diagnostic method for evaluation of subarachnoid hemorrhage in many institutions (4,5). CTA can be
performed easily and expeditiously while the patient is still on the CT table (Fig. 1). CTA is especially attractive for evaluation of critically ill patients who need emergent aneurysm surgery (3) and at centers where urgent DSA may be difficult to obtain.

CTA has the potential to provide complementary information in complex aneurysms that are difficult to evaluate with DSA, especially those in the paracclinoid location. CTA can help determine the relationship of the aneurysm to the adjacent bony landmarks and provide detailed evaluation of aneurysmal neck and dome morphology.

A 2003 meta-analysis of data on 1,251 patients with cerebral aneurysms undergoing CTA and DSA showed a sensitivity of 93.3% and a specificity of 87.8% for CTA (6). In another study of 178 aneurysms, the sensitivity and specificity of CTA were 96% and 97%, respectively (5). However, in this latter study, CTA failed to detect 7 of 11 aneurysms less than 2 mm in diameter. Moreover, there were eight false-positive findings on CTA, the source being infundibular enlargements at the origin of the posterior communicating arteries.

The combination of a high-quality CTA study and a plain CT scan demonstrating a pattern of hemorrhage consistent with the CTA-identified aneurysm may be sufficient to proceed with surgery. However, a patient with non-traumatic subarachnoid hemorrhage and a negative or equivocal CTA should be further evaluated with DSA because CTA has limited sensitivity for small aneurysms.

Carotid Atherostenosis

With modern CTA scanners, adequate visualization of the arterial tree can be obtained from the aortic arch to the circle of Willis in less than 1 minute of scan time. Analysis of pooled data from 15 high-quality studies (7) demonstrated that CTA had a mean sensitivity of 95% and a specificity of 98% for detection of more than 70% cervical carotid stenosis (7). A prospective study comparing CTA, MRA, and DSA in 44 carotid arteries showed a CTA sensitivity and specificity of 100% for the detection of more than 70% stenosis (8).

Detection of ulceration within atheromatous plaques, considered a risk factor for cerebral embolism (9), can be accomplished better with CTA than with DSA (10,11). A study by Randoux et al (8) showed that CTA and MRA were more sensitive than DSA in the detection of plaque ulceration. The inability of DSA to detect ulcerations within plaques is caused by the limited number of views typically obtained with this technique.

Calcification of atheromatous plaques limits the accurate estimation of carotid stenosis with CTA (12,13). However, this limitation can be overcome with the use of thin multiplanar volume reconstructions and transverse oblique reconstruction (8).

Stroke

A screening CT is usually performed in patients with suspected stroke to exclude intracranial hemorrhage and lesions that may mimic stroke (14). It is considered inferior to MRI, which, with a diffusion-weighted sequence, can identify acute and hyperacute infarcts with a sensitivity of 97% and a specificity of 100% (15). Moreover, the addition of a high-speed magnetic resonance perfusion study can provide valuable insight into hypoperfused brain tissue. Subtraction of the area with restricted diffusion (the infarcted

FIG. 1. Computed tomography angiography (CTA) in cerebral aneurysm. A 61-year-old woman who had undergone clipping of an anterior communicating artery aneurysm 37 years earlier presented with a sudden severe headache reminiscent of the headache experienced with the original aneurysmal hemorrhage. A. Non-contrast CT shows diffuse subarachnoid hemorrhage with hematoma in the anterior interhemispheric fissure. B. Shaded surface display of CTA reveals a bilobulated aneurysm at the junction of the A1 and A2 segments of the left anterior cerebral artery (arrows). C. Sagittal reformat of CTA demonstrates that the previously applied aneurysm clip has migrated forwards and anteriorly. The migrated clip is seen along the floor of the anterior cranial fossa (smaller arrow). The larger arrow points to residual/recurrent aneurysm at the junction of the left A1 and A2 segments.
region) from the larger area with reduced perfusion yields the region of the ischemic penumbra, the tissue at risk for further infarction that could be preserved with timely thrombolytic intervention (16).

Although MRI of stroke has these distinct advantages over other imaging techniques, the availability of magnetic resonance scanners remains limited, especially in emergent settings (17). In this circumstance, the combined use of CT, CTA, and CT perfusion in imaging of acute stroke may be quite effective (14,17). Such a combined examination can be completed within 30 minutes (14) and can offer significant information on the tissue at risk and the status of the large vessels (17). The most significant drawback of CT perfusion studies is the limited anatomic coverage. These studies presently are limited to either a 1-cm-thick or a 2-cm-thick section of tissue per acquisition; small areas of ischemia outside the planes selected for perfusion analysis could be missed. In the future, improvement in hardware and software will likely result in increased coverage of CT perfusion scans. Lev et al (18) have shown that CTA is highly accurate in the detection and exclusion of large vessel intracranial occlusion (Fig. 2). This technique therefore may be valuable in the rapid triage of stroke patients to intra-arterial thrombolytic therapy (18,19).

Vascular Injuries

The role of CTA in screening for vascular injuries associated with penetrating and blunt trauma of the neck remains uncertain because of limited data. In a prospective study of 60 patients (20) comparing the usefulness of CTA and DSA in penetrating neck injuries, CTA successfully identified 9 of 10 arterial injuries (sensitivity 90%, specificity 100%), including four arterial occlusions, two arteriovenous fistulas, two pseudoaneurysms, and one pseudoaneurysm with arteriovenous fistula. CTA missed one small pseudoaneurysm of the common carotid artery. In an earlier study by Leblang et al (21), CTA evidence of arterial injury was found in 8 of 10 patients who subsequently had injury demonstrated by DSA, with no false-positive findings in 19 patients.

CTA appears to be less favorable for the evaluation of blunt cerebrovascular injuries. In a prospective study by Miller et al (22), radiologists read 143 CTAs without knowledge of DSA findings in these patients. CTA diagnosed only 8 (47%) of 17 carotid artery injuries. CTA was falsely negative in six simple dissections, one carotid-cavernous fistula, one carotid artery occlusion, and one carotid dissection with significant stenosis. CTA also demonstrated poor sensitivity (53%) to vertebral artery injuries, missing four occlusions, two dissections with accompanying stenosis, and eight simple dissections.

In a study by Biffl et al (23), 46 patients underwent both CTA and DSA for suspected blunt cerebrovascular injuries. CTA identified 15 (68%) of 22 injuries. Six of the seven missed injuries were classified as mild (grade 1) injuries on DSA.

At this time, CTA cannot be recommended as a reliable substitute for DSA in patients with suspected blunt cerebrovascular injuries, mainly because of its inability to detect small intimal flaps and intramural hematomas. CTA has demonstrated better sensitivity and specificity in the context of penetrating trauma, but the reported patient population is small.

Other Applications

CTA has been also been used in evaluating arteriovenous malformations (24), to confirm correct clip placement.

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**FIG. 2.** CTA in intracranial arterial occlusion. A 64-year-old woman with atrial fibrillation presented with the acute onset of right weakness. **A.** CT reveals a hyperdense left middle cerebral artery (MCA), suggesting a clot in the middle cerebral artery. **B.** Shaded surface display of CTA reveals complete occlusion of the distal left M1 segment (arrow). **C.** Thick axial multiplanar reformat of CTA also displays an occluded distal M1 segment of the MCA (arrow).
after aneurysm surgery, and in detection of vasospasm after subarachnoid hemorrhage (25).

**Intracranial Venous Disorders**

CT venography (CTV), a modification of CTA, can obtain high-resolution images of dural venous sinuses and cerebral veins. For the depiction of venous anatomy, source images are obtained in the venous phase using other scanning parameters that are quite similar to CTA. Careful attention must be paid to source images, as well as to MIP images. Cerebral CTV may be superior to magnetic resonance venography (MRV) in the identification of small cerebral veins and dural sinuses and demonstrates equal sensitivity in the diagnosis of dural sinus thrombosis (26,27).

CTV is, therefore, a useful alternative to MRV. It should be considered in the evaluation of cerebral venous disorders if MRI is not possible because of metallic implants, the patient is claustrophobic or critically ill, or MRV studies are equivocal for venous abnormalities or suffer from flow/motion artifacts. The drawback of this technique, however, is the need to use ionizing radiation and iodine-based contrast media.

**MAGNETIC RESONANCE ANGIOGRAPHY**

The complex process of image generation using magnetic resonance is exquisitely sensitive to proton spins in the field of view. Moving spins in the bloodstream can be manipulated to provide intravascular signal alterations. Information can be obtained about morphology of the vessel, direction of flow, and even quantitative assessment of flow rates. A wide variety of different sequences and acquisition techniques (time-of-flight [TOF], phase contrast, contrast-enhanced 3D scanning) are available for MRA. Some techniques are complementary; more than one technique is often required to provide the necessary data for accurate diagnosis and treatment planning. Detailed discussion of these techniques is beyond the scope of this article and interested readers are referred to dedicated reviews (28,29).

Three types of MRA techniques are most frequently used in clinical practice. These include 2D and 3D TOF, phase contrast, and contrast-enhanced MRA. TOF techniques provide vascular contrast based on tagging of the longitudinal magnetization of spins flowing into a region of interest (flow-related enhancement). Using TOF methods, static tissues within a 2D slice (2D TOF) or 3D slab (3D TOF) give a low signal because of the saturation effect of a long train of closely spaced excitation pulses. An intermediate design between 2D and 3D techniques is a series of thin 3D volumes rather than a thick slab of tissue (multiple overlapping thin-slab angiography [MOTSA]). The major advantage of the MOTSA technique is its decreased sensitivity to flow-saturation effects. MOTSA is therefore the preferred sequence for evaluation of the circle of Willis.

TOF MRA techniques have been widely used for imaging of the cervical arteries in the past. Drawbacks of TOF techniques in the evaluation of cervical arteries include the small area anatomic coverage, long scan times leading to a frequent degradation of images by motion artifacts, and artificial signal loss in cases of tight stenosis because of turbulent flow. Contrast-enhanced MRA has largely overcome these limitations and is increasingly replacing TOF MRA for the evaluation of neck arteries.

Phase contrast (PC) methods produce MRA images based on motion-induced phase shifts combined with subtraction. Phase shifts are introduced to nuclei when they move in the presence of a bipolar magnetic field gradient. Phase shifts accumulated by nuclei are dependent on their velocity as well as their acceleration. By constructing an image in which the intensity is proportional to the phase shift of the nuclei, an angiographic image related to the flow properties can be created. PC MRA allows for quantification of flow velocities and flow direction. PC techniques are also very sensitive to slow flow (28). The important limitation of PC MRA techniques is the long acquisition time and the pronounced loss of signal in areas of disturbed flow. For these reasons, PC MRA techniques are seldom used in clinical practice. Their main use is in the quantitative evaluation of flow velocities and flow direction in research studies.

More recently, contrast-enhanced MRA (CE MRA) techniques have been adopted in the evaluation of the extracranial arterial system. These techniques depend on shortening of the T1 signal by intravenous administration of gadolinium-based contrast agents. With the T1 of blood reduced to less than 50 ms, very heavily T1-weighted images can be acquired in which blood has high signal intensity relative to the saturated surrounding tissues. The timing of contrast injection and imaging acquisition are crucial. The sequence must be performed before the venous phase to achieve relative suppression of venous signal intensity. Although CE MRA has now become the technique of choice in the assessment of extracranial vessels, it is not considered optimal for evaluation of intracranial arteries because of its relatively low spatial resolution.

**Carotid Atherostenosis**

Although the major clinical trials related to surgical management of carotid atherosclerotic disease have used selective DSA for determination of the degree of extracranial carotid artery stenosis (31,32), MR imaging has emerged as a viable alternative.

Technical evolution from 3D TOF MR techniques to CE MRA has largely overcome the historical overestimation of stenosis by MR (33). Several trials have shown CE
MRA sensitivities ranging from 86% to 100% and specificities ranging from 85% to 96% in the detection of significant carotid stenosis (34). Recent studies have also shown that ulcerations are more frequently identified with CE MRA or CTA than with DSA (8, 35).

However, MRA has a lower specificity in the detection of carotid stenosis than DSA because of lower spatial resolution and signal loss in areas of high-grade stenosis as the result of flow turbulence. On occasion, artifact from a hemorrhagic plaque may result in underestimation of the severity of stenosis. Even so, the introduction of CE MRA has now replaced DSA in assessment of atherosclerosis in many centers (34).

Stroke

In recent years, rapid advances have been made in the MR imaging of acute stroke. A combination of diffusion-weighted imaging and perfusion-weighted imaging has been used in numerous studies to delineate the ischemic penumbra.

Previous studies indicated that nearly one-third of patients with acute major stroke have no demonstrable vessel occlusion on DSA (36) and thus may not benefit from thrombolytic therapy. The combination of MOTSA and CE MRA provides a non-invasive and sensitive way to exclude intracranial vascular occlusions and to detect potential concomitant carotid abnormalities.

Ohue et al (37) evaluated six acute stroke patients studied with MRA and DSA before thrombolysis. In all patients, MRA clearly demonstrated the occluded arteries. MRA findings correlated well with the findings on DSA. Among 30 patients who had had acute stroke, Kenton et al (38) compared the ability of transcranial color Doppler and MRA in identifying circulatory changes after stroke. They concluded that both modalities yielded useful information but that MRA was better in demonstrating fine vessel detail.

Intracranial Aneurysms

The role of magnetic resonance in the detection of intracranial aneurysms continues to evolve. MRI suffers from lack of sensitivity for detection of acute subarachnoid hemorrhage, but MRA has high sensitivity and specificity for detection of aneurysms in the setting of subarachnoid hemorrhage (29, 40). However, it is often difficult to obtain MRA in acutely ill patients on an urgent basis. Therefore, CT combined with CTA is preferable to MRA in the acute setting (28).

MRI combined with MRA holds great promise for evaluation of unruptured aneurysms. The non-invasive nature of MRA and the lack of need for ionizing radiation or intravenous contrast make it ideal for screening asymptomatic patients at high risk for aneurysm (28). High-risk populations include those with polycystic kidney disease, Ehlers-Danlos syndrome, cerebral arteriovenous malformations, fibromuscular dysplasia, coarctation of the aorta, and a strong family history of intracranial aneurysms.

Arteriovenous Malformations and Dural Arteriovenous Fistulas

MRA has been used extensively as an adjunct in the evaluation of arteriovenous malformations. Clinically important information concerning arterial feeders, nidus location, draining veins, flow direction, and flow velocity can be obtained from MRA studies (28). However, poor temporal or phasic resolution and the inability to visualize the pattern of segmental blood supply preclude its use as a replacement for DSA. Other important limitations of this technique include a signal void within tortuous feeding arteries created by complex flow, the inability to differentiate flow from methemoglobin within a subacute hematoma, and the lack of visualization of slow venous flow as a result of progressive-spin saturation (41).

The diagnostic capability of MRI and MRA for dural arteriovenous fistulas (AVFs) remains uncertain. Spin-echo MR detects only 15% of AVFs (28, 42) and poorly defines their exact location. In this regard, Noguchi et al (42) have addressed the usefulness of combined 3D TOF and CE MRA. In their study, multiple areas of high signal intensity adjacent to the sinus wall findings were observed in all cases of dural AVF on 3D TOF MRA. The sensitivity and specificity of this sign (multiple high-intensity structures adjacent to the sinus walls) was 100%. These high-intensity curvilinear or nodular structures adjacent to the sinus wall likely represent the meningeal branches of the feeding arteries. In 13 of their 15 patients, findings of early filling of the venous sinuses were observed on CE MRA.

TOF MRA has been also studied as a tool for detection of residual or recurrent AVFs after treatment. In a study of 14 previously treated patients with cavernous dural AVF by Hirai et al (43), MRA had a sensitivity of 100% and a specificity of 80% in the detection of residual/recurrent AVF.

The source images of 3D TOF MRA are more useful than the MIP images in the diagnosis of dural AVF because these source images are able to display tiny vascular pedicles that may be lost during the processing of MIP images (28).

Cervicocranial Arterial Dissections

Although DSA can detect luminal narrowing, irregularity, occlusion, and pseudoaneurysms associated with dissections, the same findings may be depicted on MRA. Moreover, MRA has the added advantage of being able to directly visualize the vessel wall, including intramural hematomas (44) (Fig. 3). Using DSA as the gold standard in patients with carotid dissection, Levy et al (45) have shown...
CT and MRA in Cervicocranial Vascular Disease


FIG. 3. Magnetic resonance imaging and magnetic resonance angiography in vertebral artery dissection. A 32-year-old man had acute onset left neck pain and dizziness. A. Axial T1W magnetic resonance imaging of the neck reveals a crescentic hyperintensity in the wall of left vertebral artery suggesting an intramural hematoma (arrow). B. Time-of-flight magnetic resonance angiography demonstrates vessel caliber change and a well-defined intimal flap (arrows).

A sensitivity and specificity for MRI of 84% and 99% and for MRA of 95% and 99%, respectively. MRI and MRA are also helpful in follow-up of patients with carotid dissections by monitoring the resolution of an intramural hematoma or early detection of complications of dissection (28).

The role of MRI and MRA in the evaluation of vertebrobasilar dissections is evolving. Levy et al (45) reported a sensitivity and specificity of 20% and 100% for MRA and 60% and 58% for MRI in the detection of vertebrobasilar dissections. However, better sensitivity has been reported by other authors (44,46). At our institution, MRI combined with MRA is the method of choice for evaluation of suspected carotid and vertebrobasilar dissections. We reserve CTA or DSA for equivocal MR results and for those who are unable to undergo an MR examination.

Cerebral Venous Disorders

MRV has replaced DSA for the evaluation of venous thrombosis (47). The venous system has traditionally been evaluated with the 2D TOF technique. However, drawbacks of this method include incorporation of the high signal intensity of methemoglobin within a thrombus that can mimic flow on MRA. In addition, non-uniform flow and in-plane flow within the sinuses can result in artifactual areas of filling defects (clots) or stenosis within the sinuses (Fig. 4). Addition of the PC technique can help to avoid these pitfalls (28).

More recently, 3D CE MRV has become a valuable addition for the evaluation of intracranial venous disease (47). Distinct advantages of this technique over TOF and PC techniques are superior vessel depiction, greater suppression of background signal, and substantially shortened...
CHOOSING THE APPROPRIATE TEST: CTA VERSUS MRA VERSUS DSA

The choice of the imaging test (Table 1) depends on patient characteristics, the disease condition, the availability of technique and equipment, and the preference of the interpreting physician. Increasingly, CTA and MRA are replacing DSA in the evaluation of many cervicocranial vascular disorders. Evaluation of stroke, atherosclerotic carotid disease, and venous disorders is easily accomplished by either MRA or CTA; the choice depends on individual preference. DSA is mainly used as a problem-solving technique when the CTA/MRA findings are equivocal or not consistent with clinical symptoms.

CTA is preferred for evaluation of critically ill patients such as those with subarachnoid hemorrhage. It may be used as the first-line imaging modality in claustrophobic patients with suspected stroke, carotid stenosis, or venous disease or in those who have other contraindications to magnetic resonance. Unlike MRA, CTA can provide information about the presence of calcifications within the atherosclerotic plaques, a feature that may be valuable to the physician performing angioplasty. Another area in which CTA is superior to MRA is in depiction of the relationship of intracranial aneurysms to adjacent bony structures.

However, because MRA does not involve the use of ionizing radiation, it is preferred for younger patients. MRA is also used preferentially in patients with impaired renal function, because CTA requires large amounts of potentially nephrotoxic iodinated contrast media. MRA is the test of choice in screening for cerebral aneurysms and evaluation of dissection of cervicocranial vessels. CTA is continuing to improve, but currently this technique must be considered investigational in the assessment of dissection and any traumatic vascular lesion.

DSA is still the “gold standard test” for the evaluation of arteriovenous malformations, arteriovenous fistulas, and for demonstrating small vessel alterations in patients with vasculitis. A large number of centers, including our own,

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<th>Carotid athero-stenosis</th>
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<td>Blunt neck injuries</td>
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<td>Penetrating neck injuries</td>
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<tr>
<td>Venous disorders</td>
<td>1. MRV (preferably contrast enhanced)</td>
<td>DSA (largely reserved for problem solving and for thrombolytic therapy)</td>
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<td>2. CTV</td>
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* Preferred tests have been ranked in the order of usefulness.

CTA, computed tomography angiography; CE MRA, contrast-enhanced magnetic resonance angiography; DSA, digital subtraction angiography; MOTSA, multiple overlapping thin-slab angiography; DWI, diffusion-weighted imaging; PWI, perfusion-weighted imaging; AVM, arteriovenous malformation; AVF, arteriovenous fistula; MRI, magnetic resonance imaging; CTV, computed tomography venography.
continue to use DSA as the standard test for evaluation of subarachnoid hemorrhage. However, it is reasonable to use CTA in place of DSA in these patients as long as the potential pitfalls of CTA are understood. These include relative insensitivity for the detection of aneurysms smaller than 3 mm and thrombosed aneurysms. It may be difficult on CTA to distinguish between an infundibular dilatation at the posterior communicating artery origin and true aneurysm. If there is any doubt about the diagnosis, DSA should be performed for further clarification.

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Magnetic Resonance Imaging of Suspected Cervicocranial Arterial Dissections

Gaurang V. Shah, MD, Douglas J. Quint, MD, and Jonathan D. Trobe, MD

Abstract: The authors propose that the optimal screening protocol for evaluation of suspected cervicocranial arterial dissections is magnetic resonance imaging (MRI) that includes three components: 1) contrast-enhanced three-dimensional time-of-flight magnetic resonance angiography (MRA) through the superior mediastinum, neck, and skull base; 2) three-dimensional multiple overlapping thin-section acquisition MRA of the skull base and Circle of Willis region; and 3) axial non-contrast, non-fat-suppressed T1-weighted, fat-suppressed T1-weighted, and T2-weighted spin-echo MRI from the level of the aortic arch through the level of the circle of Willis. MRA permits visualization of vascular luminal narrowing or obliteration, which can suggest vascular dissection but can also be caused by congenital variation, dysplasia, intraluminal thrombus, vasospasm, or extramural compression by tumor. By directly visualizing the blood vessel wall, axial T1-weighted and T2-weighted spin-echo MRI can identify the intramural hemorrhage of vascular dissection. This protocol is designed to maximize the sensitivity of a noninvasive technique and may eliminate the need for conventional endovascular angiography.

(J Neuro-Ophthalmol 2004;24: 315-318)

Cervicocranial (carotid and vertebral) arterial dissection is among the most common causes of ischemic stroke in patients aged younger than 50 years (1). There is a premium on early diagnosis because short-term antiplatelet or anticoagulant therapy may be useful in preventing stroke (2). Dissections of the carotid and vertebral arteries can be detected by many imaging methods, but there is yet no consensus on the most efficient and effective choice. We propose that a combination of spin-echo magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) is an accurate screening tool and may eliminate the need for conventional endovascular angiography. Based on recent clinical experience, we have the impression that clinicians are not optimizing the use of this modality.

CASE REPORT

Headache and falling to his right suddenly developed in a 42-year-old man. Clinical findings included a right Horner syndrome; nystagmus; skew deviation; left palatal deviation; poor swallowing, speech, and right extremity ataxia; as well as right facial and left extremity pain and temperature loss. These findings were considered typical of a right dorsolateral medullary and possibly cerebellar infarct in the distribution of the right posterior inferior cerebellar artery; in other words, a Wallenberg syndrome.

Four hours after onset, computed tomographic (CT) (Fig. 1A) scanning revealed a low attenuation area in the right inferior cerebellum with minimal associated mass effect. Intracranial MRI obtained the next day (Fig. IB) showed high T2 and fluid-attenuated inversion recovery signal, as well as restricted diffusion (Fig. IB) in the right inferior cerebellum and the right dorsolateral medulla consistent with subacute infarction.

Skull base and intracranial MRA with three-dimensional (3D) multislice overlapping thin-section acquisition performed on the day of admission demonstrated absence of the intracranial (V4) segment of the right vertebral artery (Fig. 1C). The contrast-enhanced 3D time-of-flight MRA of the superior mediastinum and neck (Fig. 1D) showed narrowing and tapering of the right vertebral artery involving the V2 segment (where the vessel enters the foramen transversarium at the C6 level) with complete absence of vessel signal above the lower C3 level.

Although these studies disclosed a right vertebral vascular abnormality, they did not distinguish between vascular dissection and other potential causes of luminal compromise such as congenital variation or dysplasia, intraluminal thrombosis, vasospasm, or extramural compression by tumor. Therefore, the patient was recalled to the MR scanner the next day for axial fat-suppressed T1-weighted imaging (Fig. 2A), which showed a high signal area indicating methemoglobin-containing thrombus within the wall of the V2 segment of the right vertebral artery. The subacute nature of the thrombus was confirmed on the axial T2 MRI...
FIG. 1. A. Axial non-contrast CT imaging in a patient with symptoms consistent with an acute right dorsolateral medullary infarct shows a hypodense area in the inferior portion of right cerebellar hemisphere suggestive of infarction in the right posterior inferior cerebellar artery territory. B. Axial diffusion-weighted magnetic resonance imaging (MRI) demonstrates restricted diffusion of the inferior portion of right cerebellar hemisphere and also the dorsolateral right medulla (arrow) consistent with acute/subacute infarction. The medullary component of the infarct was not visualized on computed tomography (CT) because of beam-hardening ("streak") artifacts and the intrinsic lower sensitivity of CT when compared with MRI in evaluating the posterior fossa. C. Maximum intensity projection magnetic resonance angiogram (MRA) of brain vessels with three-dimensional (3D) multislice overlapping thin-section acquisition demonstrates absent signal in the expected location of the intracranial (V4) segment of the right vertebral artery (arrowheads). D. Contrast-enhanced 3D time-of-flight MRA through the neck demonstrates narrowing and tapering of the right vertebral artery at the V2 segment (arrowheads).

(Fig. 2B) because increased intramural T2 signal was seen in the same region. Absence of right vertebral arterial blood flow was also confirmed on these images (Figs. 2A and B) because the normal “flow void” was absent in the expected location of the vertebral artery.

The diagnosis of vertebral artery dissection prompted immediate anticoagulation with heparin and later warfarin. Within 3 months, the patient’s clinical manifestations had largely resolved. Repeat MRI showed normal luminal morphology, so the anticoagulation was discontinued.

Our patient presented with classic symptoms of dorsolateral medullary and cerebellar infarction (3). Initial intracranial imaging demonstrated the changes of subacute ischemic infarction. MRA showed absence of the distal (intracranial) right vertebral artery (Fig. 1C). However, initial neck evaluation included only MRA (without MRI), which revealed tapering and complete occlusion of the cervical portion of the right vertebral artery (Fig. 1D). This finding was not specific for a cause of the observed vascular occlusion. Only after recalling the patient to the scanner and obtaining axial spin-echo MRI was an intramural hematoma identified. This finding confirmed dissection as the cause of the vertebral arterial occlusion.

PROPOSED IMAGING PROTOCOL

In the evaluation of suspected cervicocranial dissection, the proper combination of MRI and MRA offers the best diagnostic screening tool currently available, even though endovascular angiography has long been considered the gold standard (4,5). As with endovascular angiography, MRA can sometimes identify dissection of cervical arteries by demonstrating specific luminal abnormalities such as aneurysmal dilatation or an intimal flap (6), which may be better visualized on the “source images” (the images from which MRA reformatted images are generated) than on the reformatted maximum intensity projection, the MRA images most familiar to clinicians (4). Earlier reports had suggested that MRA was not as sensitive to vertebral artery dissection as to carotid artery dissection caused by the smaller lumen and physiological variations in the caliber of vertebral artery (7), but subsequent studies have disputed that notion (4,8).
FIG. 2. A. Axial non-contrast, fat-suppressed, T1-weighted MRI obtained 2 days after the MRI demonstrates high signal within the lumen of foramen transversarial (V3) segment of the right vertebral artery, compatible with the subacute (methemoglobin phase) intramural thrombus (arrow). Note the normal appearance of the left vertebral artery (arrowhead). B. Axial non-contrast T2-weighted MRI shows that the expected normal “flow void” has been replaced with high signal within the lumen of the right vertebral artery at the same anatomic level as in A (arrow). Note the normal appearance of the left vertebral artery (arrowhead). C. Axial non-contrast, T1-weighted MRI obtained after a few months shows persistent lack of normal “flow-void” signal in the right vertebral artery with a concentric high signal around the lumen of the artery (arrow). Compare with normal flow void of the left vertebral artery (arrowhead).

However, neither endovascular angiography nor MRA can directly identify a dissection unless a double-lumen, intimal flap, or dissecting aneurysm is found. Narrowing or even obliteration of the vascular lumen can have many causes (8), including congenital variation, dysplasia, intraluminal thrombosis, vasospasm, or extramural mass. To differentiate dissection from these other causes, one must be able to directly visualize the vessel wall, which is possible with MRA but not usually possible with endovascular angiography.

The typical MRI appearance of a dissected blood vessel in cross-section is increased diameter of the artery with eccentric narrowing of the arterial lumen caused by the presence of an intramural hematoma (9–11). The shape of the intramural hematoma varies with the relationship of the imaging plane to the axis of the dissected vessel (4). The hematoma may be crescentic, oval, or circumferential (8,12,13).

The signal intensity of an intramural hematoma on T1-weighted images depends on the age of the hemorrhage (9,14). The T1 signal appears essentially isointense for the first few days after bleeding occurs (“deoxyhemoglobin phase”) and then becomes hyperintense in the subacute stage (“methemoglobin phase”). The abnormal signal persists for a few months (15), but disappears as the intramural blood is absorbed (15,16). A follow-up MR examination with the proposed protocol showed concentric intraluminal high T1 signal in the right vertebral artery (Fig. 2C). Because the high T1 signal of intramural thrombus in the subacute (methemoglobin) phase can blend with surrounding fat on conventional spin-echo T1-weighted images, fat-suppressed T1-weighted scan techniques (17,18) are used to better delineate subacute hematomas (19). However, sometimes these images can be degraded because of artefacts. T2-weighted imaging is performed to confirm the intramural hematoma in the acute phase (isointense T1 signal with a decreased T2 signal (8)), and also to better demonstrate either a residual patent but narrowed vascular “flow void” or complete lack of intraluminal blood flow. Therefore, we believe that the ideal imaging evaluation of a patient clinically suspected of dissection of the cervicocranial arteries consists of a combination of axial noncontrast nonfat-suppressed T1-weighted and fat-suppressed T1-weighted images, together with T2-weighted spin-echo MRI and contrast-enhanced 3D time-of-flight MRA through the superior mediastinum, neck, and skull base, and 3D multislice overlapping thin section acquisition MRA of the skull base and circle of Willis region.

These imaging principles apply equally to diagnosis of carotid artery dissection. We recently encountered a patient in whom high signal in carotid artery wall on axial MRI disclosed the diagnosis of carotid artery dissection in the presence of a minor MRA luminal abnormality that had been dismissed as a normal variant. A 53-year-old man with the acute onset of left-sided headache and a left-sided Horner syndrome underwent a contrast-enhanced time-of-flight MRA (Fig. 3A), which showed only subtle asymmetry of the internal carotid arteries. The study was interpreted as normal. His clinical findings were therefore attributed to cluster headache syndrome. However, a subsequent T1 axial neck MRI revealed the high signal of intramural hemorrhage expanding the vessel wall and consistent with dissection (Fig. 3B).
Ultrasound has been advocated for the evaluation of suspected cervicocranial dissection. A study of suspected cervical carotid dissection 15 years ago reported a sensitivity of 76% (20). The diagnosis is suggested by an intense systolic low-frequency Doppler signal of alternating flow direction along the extent of a tapered lumen or proximal to severe obstruction at the skull base. (20). In another study, lack of diastolic flow in a vertebral artery suggested dissection with a sensitivity of 79% (8). However, evaluation of vertebral arteries with ultrasound is hampered by the fact that sound waves cannot penetrate the osseous structures surrounding the foramina transversaria between C6 and C2 (V2 portion of the vertebral arteries). Moreover, ultrasound is unreliable for luminal compromise of less than 50%, cannot reliably visualize intramural abnormalities, and cannot evaluate any vessels in the superior mediastinum, behind the mandible, within the skull base, or within the intracranial compartment.

With the advent of multidetector helical CT scanners, CT angiography has emerged as a potential rapid alternative in the screening of cranio-cerebral vascular disease (21, 22). It can reveal a narrowed arterial lumen with enlargement of the overall vessel diameter caused by intramural hematoma. However, subtle intimal flaps can escape detection with CT angiography (22). Its role in this setting will be defined with further experience.

REFERENCES
More than 360 neuro-ophthalmologists from 36 countries gathered in Geneva, Switzerland from July 18 to 22, 2004 to attend the 15th International Neuro-Ophthalmology Society (INOS) meeting. It was the largest attendance at INOS, which began modestly in 1976 with 58 people convening at the picturesque Chateau de La Napoule near Cannes under the auspices of Thomas R. Hedges, Jr.
Drs. Hedges and Huber opened the meeting with a nostalgic recall of their chance encounter in a breakfast line at the 1975 Annual Meeting of the American Academy of Ophthalmology in Dallas, Texas, where they hatched the plans for INOS. They paid tribute to this year’s organizer, Avinoam B. Safran, MD, the chairperson of the ophthalmology department of the University of Geneva. The kudos were well-deserved. The meeting was held in a gorgeous modern conference center that had been recently vacated by United Nations delegates. The lecture hall was appointed in luxurious leather chairs (fauteuils, really), microphones at each seat, and video blow-up of the speaker. Dr. Safran had recruited an audiovisual team immunized against all manner of media viruses to deftly handle the complexities of modern multimedia projection. There were 96 oral presentations delivered in the conference chamber and 114 posters displayed in the halls around it.

FIG. 4. Doodles by Anonymous during the proceedings.

FIG. 5. Detlef Kompf, MD (Lübeck, Germany) chats with Alfred Huber, MD, and Thomas R. Hedges, Jr, MD, the founders of INOS, at the opening night cocktail party on the battlements of the old city of Geneva.

FIG. 6. The Cathedral of Geneva, a symbol of the old Calvinist tradition, rises above the lakeshore banks and watchmaking buildings, symbols of the new Calvinist tradition.

FIG. 7. The INOS Council at the 2004 INOS Meeting. Front row (left to right): William F. Hoyt, MD (San Francisco, CA), Avinoam B. Safran, MD (Geneva, Switzerland), Alfred Huber, MD (Zürich, Switzerland), Masato Wakakura, MD (Tokyo, Japan); back row (left to right): Guntram Kommerell, MD (Freiburg, Germany), Neil R. Miller, MD (Baltimore, MD), Christopher Kennard, MD (London, England), Roberto Ebner, MD (Buenos Aires, Argentina), James A. Sharpe, MD (Toronto, ON, Canada), Bertil Lindblom (Mölndal, Sweden).
The imaginative Dr. Safran gathered the oral presentations into seven symposia, each named in honor of a physician–scientist who had made a seminal contribution to the topic and who (coincidentally!) had a strong historical connection to Geneva. The symposia were anchored with invited state-of-the-art lectures and colorful historical vignettes about the life and achievements of the honoree. So, there was the Georges de Morsier Symposium on anterior visual pathways, the Louis Albert Necker Symposium on imaging techniques, the Charles Bonnet Symposium on higher visual function, the Otto Loewenstein Symposium on pupil function, the Leon Revilliod Symposium on eye and lid movements, the Adolphe Franceschetti Symposium on systemic disorders, and the Henry Dunant Symposium on pain.

As usual, the social events were a highlight of the INOS. On the first evening, congregants were bussed to Geneva’s cantonal Hotel de Ville, where councilors have met continuously since the beginning of the 17th century. After a greeting from the mayor in the historic courtyard, and a pause in the light drizzle, a string quartet zestily delivered Haydn and Schumann. Cocktails were then served.
in the nearby esplanade atop the old city wall where can­
nons guarded the city against the predatory Savoyards. On
the second day, attendees met at the museum of the Red
Cross founded 150 years ago même à Genève. The next
day, there were excursions to the famous Château de
Chillon (where Byron was inspired to write his famous
poem “The Prisoner of Chillon”), to Mount Chamonix, to
the vieille ville of Geneva, or to the recently opened Patek-
Philippe museum, which features more than 2,000 treasures
of Geneva’s renowned watchmakers, known as “la Fab-
rique.” The meeting ended gloriously with a dinner at the
elegant Hôtel Beau Rivage, which fronts on Lake Geneva
(also known as Lac Léman) and has entertained dignitaries,
including President Woodrow Wilson, during the found­
ing in Geneva of the League of Nations after World War I.
As we gazed out onto the lake’s splendid jet d’eau, the
symbol of modern Geneva, and dined on terrine of candied
Provençal vegetables, fried ferra fillet, and mille-feuille
of seasonal fruits, we were enthusiastically beckoned by
Masato Wakakura, MD (Tokyo, Japan) to the 16th INOS
Meeting, which will be held November 29 to December 2,
ne.jp/inos2006/ or inos@secretariat.ne.jp). The e-mail ad-
dresses of all INOS 2004 attendees will be sent soon to all
INOS members and attendees.

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Acknowledgment
Thanks to Helmut Wilhelm, MD (Tubingen, Ger-
many) for many of the photographs.
Approximately 5,600 abstracts were presented at the Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO), Fort Lauderdale, FL, April 25 to 29, 2004. The abstracts, available at www.arvo.org, are referenced by program number (#).

NEUROPROTECTION: RETINAL GANGLION CELLS

New approaches to neuro-protection that target the optic nerve or the retinal ganglion cells (RGCs) in animal models and of optic nerve damage in patients were the subject of a symposium, platform presentations, and posters. Emphasis was on new mechanisms, new therapies, and clinical trials. In one paper (#20), activation of caspases and changes in transcription factor expression led to a shift in anti-apoptotic protein levels within hours after axotomy. Insulin-like growth factor and brain-derived neurotrophic factor, erythropoietin, caspase inhibitors, and anti-sense oligos (such as BAX anti-sense) were found to have neuroprotective activity in this optic nerve injury paradigm. In another study (#21), a 15-kD rod-dependent cone viability factor expressed in the outer nuclear layer of the normal retina rescued the rd1 mutant phenotype mouse (a model of photoreceptor protection in retinal dystrophies) and increased cone viability in vitro. Although intravitreal injection of neurotrophins such as brain-derived neurotrophic factor can extend the life of RGC neurons, their use is limited because of a short half-life in vitro, adverse effects, and because they are not cell-specific modulators of function. In an experimental study (#22), signaling pathways stimulated by TrkB, MAP kinase, and AKT kinase appeared to be appropriate targets for neuroprotection. In that study, optic nerve injury led to down-regulation of TrkB receptors in RGCs. Up-regulation of TrkB by adenovirus transfection of RGCs, together with stimulation with brain-derived neurotrophic factor, led to a prolonged life for RGCs.

Other neuroprotective agents were found to prevent RGC degeneration or promote survival of retinal cells in animal models (#827, 832, 835, 838, 843, 873, 881, 884). The agents were citicoline (cytidine-5-diphosphocholine), lithium chloride, autocamtide-2-related inhibitory peptide (AIP, a specific inhibitor of calcium/calmodulin-dependent protein kinase II), polyethylene glycol-conjugated superoxide dismutase, Akt activation (protein kinase B), ciliary-derived neurotrophic factor, calcium channel blockers (nimodipine, lomerizine, iganidipine), lataroprost, and edaravone (3-methyl-1-phenyl-5-one, a free radical scavenger).

Microglia, the resident immune cells in the brain and the eye, serve immune-related functions. Partial crush injury of the optic nerve leads to primary and secondary degeneration. In this process, T lymphocytes are attracted to the optic nerve. Autoimmune T cells protect neurons from secondary degeneration. In the absence of T cells, elevated intraocular pressure causes a greater loss of neurons. Immunization with retinal proteins that are associated with experimental autoimmune uveitis protects against glutamate toxicity. CD4+ and CD25+ T cells control the ability to elicit an autoimmune response. These findings suggest a rationale for boosting autoimmunity in CNS repair models. One example is the weak agonist activity of a self-antigen such as glatiramer acetate (Copaxone), a polypeptide used in the treatment of multiple sclerosis. Glatiramer acetate was found to decrease RGC loss in an experimental model of glaucoma (#23). Glatiramer-activated T cells home to the damaged site, cross-react weakly with retinal antigens, and are locally activated, producing cytokines and neurotrophic factors that enhance microglial uptake of glutamate. Therefore, vaccination with self-antigens such as glatiramer acetate may alter disease progression (#23). Challenges and issues on the design and conduct of clinical trials of neuroprotections using NMDA, AMPA, beta-1 antagonists, alpha-2 agonists, and nitric oxide synthase inhibitors were discussed (#24). Other challenges included a lack of validated endpoints, the slow nature of the neurologic disease, and the high costs of trials.

OPTIC NEUROPATHY

A rat model of anterior ischemic optic neuropathy demonstrated a 42% loss of axons when compared with controls 3 months after application of an argon green laser beam to the optic nerve (#1585). This study provided a timeline of axonal loss essential to the study of potential neuroprotective agents. In a retrospective review of 32 cases of traumatic optic neuropathy (#1606), the authors...
concluded that the degree of visual impairment on initial presentation predicted the likelihood of visual improvement. Loss of consciousness was correlated with a lower frequency and extent of visual recovery. Latency from the traumatic event to the initiation of corticosteroid treatment did not appear to significantly affect outcome. In a review of 55 cases of amiodarone-associated optic neuropathy (1613), 88% occurred within 12 months of starting amiodarone, 13% were asymptomatic, 40% presented with sudden vision loss, 47% had insidious vision loss, 18% progressed to legal blindness (visual acuity of 20/200 or less), 91% had visual field loss, 40% had color vision loss, and 85% had disc edema. The authors concluded that amiodarone-associated optic neuropathy can be classified into the following five subtypes in order of decreasing frequency of presentation: insidious onset, acute-onset, retrobulbar, raised intracranial pressure, and delayed progressive onset. Most cases start within 12 months of initiating amiodarone. Visual acuity loss may not be permanent, but visual field loss usually is.

**RETINAL AND OPTIC NERVE IMAGING**

There were many presentations on advances in retinal and optic nerve imaging that emphasized improved resolution and speed. The ultrahigh speed spectral domain optical coherence tomography (OCT) is 75 times faster and has twice the resolution of standard OCT, which allows for comprehensive 3-dimensional volume rendering of the optic nerve and fovea within 10 seconds (1139). A new method of stabilized Doppler flowmetry using tracking scanning laser ophthalmoscopy provides dynamic dye-free angiographic images of retinal blood flow in response to visual stimuli (1137).

Several papers discussed the reproducibility of optic nerve head parameters and retinal nerve fiber layer thickness measurements using the new OCT 3 device (1629, 1623), ultrahigh resolution OCT (2176), scanning laser polarimetry (1625), and Heidelberg Retinal Tomography scanning laser ophthalmoscopy (1619, 51). Confocal and multiphoton microscopic imaging techniques were used to obtain new information about the spatial and temporal events that occur during the course of ocular vascular disease (486).

The first direct visualization of individual RGCs undergoing apoptosis in vivo in the glaucoma primate model (stratosporine-induced RGC apoptosis) was very elegantly demonstrated using intravitreal fluorescent-labeled annexin-5 and confocal scanning laser ophthalmoscopy (1114).

**NEUROIMAGING**

Metabolic imaging with fluorodeoxyglucose positron emission tomography demonstrated functional changes in the primary visual cortex and visual association areas in all eight patients with non-arteritic ischemic optic neuropathy. Treatment with pentoxifylline for 3 months reversed the changes observed in the brain in six of the eight patients (249). Brain activation maps measured in nine volunteers using functional magnetic resonance imaging demonstrated that central filling-in of an artificial central scotoma was accompanied by increased neuronal activity in the primary visual cortex, suggesting an active cortical process (247). Computed tomography angiography was shown to be an accurate, sensitive, noninvasive test for delineation of high-flow cavernous sinus lesions (257).

**IDIOPATHIC INTRACRANIAL HYPERTENSION**

Because arachnoid granulations may be the site of outflow resistance of cerebrospinal fluid in idiopathic intracranial hypertension (IIH), a group of investigators developed an in vitro model using arachnoid cap cells. They used an immunomagnetic technique to separate human arachnoid granulations in culture to study cerebrospinal fluid flow characteristics (28). This model successfully obtained pure cultures of pia–arachnoid cells that will allow study of fluid dynamics and the responses of drugs used to treat IIH. The amide II wavelength free electron laser was used to make a 2-mm-diameter optic nerve sheath fenestration in blind patients undergoing enucleation that resulted in cerebrospinal fluid release and an effective optic nerve sheath incision. Tissue glial response was similar to that after incision by scissors. No acute damage or thermal damage to the optic nerve was found (45). Heidelberg Retinal Tomography II was used to measure surface topography (neuroretinal rim and peripapillary surface height), whereas retinal nerve fiber layer thickness was measured using the OCT 3 in 24 eyes of 12 women with IIH. Although the elevation of surface height during optic disc swelling was associated with an increase in nerve fiber layer thickness, the association was weak. Factors other than swelling within the retinal nerve fiber layer must play a role in the elevation of the optic nerve head in IIH (1626).

**NEUROTROPHIC KERATITIS**

A combination of parameters including central corneal sensation (measured by the Cochet-Bonnet esthesiometer) and aqueous tear production (measured by the Schirmer test) was found to be useful in assessing the risk and progression of neurtrophic keratitis in 277 patients (2955). A distinct variant of neutrophic keratitis called "noninfectious pseudodendritic keratitis" that resembled dendritic herpes zoster or herpes simplex keratitis was described in nine patients undergoing anti viral therapy. The lesions were located inferiorly in the cornea and demonstrated a rapid response to punctal occlusion (2954).
LEBER HEREDITARY OPTIC NEUROPATHY

A separate session dedicated to Leber Hereditary Optic Neuropathy (LHON) detailed the results of a comprehensive 2-year follow-up examination of the 300-member homoplasmic 11778 LHON pedigrees of seven generations in rural Brazil. Ongoing studies with the asymptomatic carriers of 11778 mutation in this pedigree showed that subclinical disease reflects ongoing low-grade degeneration. Decreases in red/green and blue/yellow chromatic and luminance spatial contrast sensitivity were observed in 11778 mutation asymptomatic carriers. Cambridge color testing demonstrated that 40% of carriers had loss of color discrimination, mostly in the protan and deutan axes (#1012). Multifocal ERG studies in 29 asymptomatic carriers and four affected LHON patients showed substantial abnormalities in peripapillary ganglion cell function. Multifocal visual evoked potential (VEP) abnormalities were subtle and difficult to detect (#1015). OCT studies on NFL thickness in patients with LHON suggest that the NFL has increased thickness in patients at less than 6 months from the time of acute vision loss (#1010). In contrast, color vision testing in affected LHON patients demonstrated a profound loss in the red–green system, whereas the blue system (tritan axis) was relatively spared (#4331).

An experimental study designed to investigate the influence of bioenergetic failure in driving the pathway of apoptotic cell death in cybrid cells bearing the LHON mutation revealed that the LHON mutation profoundly impairs complex I-dependent synthesis of ATP and that LHON cybrid apoptotic death in galactose is caspase-independent (#1624).

ELECTROPHYSIOLOGY

In an attempt to prevent the posterior ischemic optic neuropathy associated with spine surgery, optic nerve function was evaluated in three patients using intraoperative flash VEPs during spine surgery under total intravenous anesthesia. There was a trend toward increased stability of VEP waveforms in all parts of surgery under total intravenous anesthesia, with all waveforms identifiable throughout the surgery using a certain combination of general anesthetics (#251). Multifocal VEP recordings showed local delays in 11 of 12 patients with atypical optic neuritis (#242). This technique was found useful in diagnosing psychogenic static perimetry defects (#245).

PUPIL

Forty-nine normal subjects and 46 patients with asymmetric visual field loss caused by prechiasmal defects were used to compare the diagnostic power of timing parameters and the amplitude of pupil contraction (#230). This study found that the timing of the pupil reflex had greater diagnostic power. In an experimental study on the macaque monkey, melanopsin-containing ganglion cells contributed significantly to light-evoked pupillary responses over much of the photopic range (#2262). A relative sparing of the pupillary light reflex was seen in seven patients with ischemic optic neuropathy. These results suggested that ganglion cells related to the pupillary reflex were less affected than those related to vision in eyes with ischemic optic neuropathy (#250).

PERIMETRY

Subtle visual field defects not detected by conventional perimetry were detected by a recently developed program that uses tiny points of light as stimuli (RAREBIT). This technology identified the eye with the afferent pupil defect in five of five cases, all of which had normal Humphrey visual field 24-2 tests (#234). Among 15 patients with glaucomatous optic neuropathy who underwent Humphrey 24-2 achromatic automated perimetry, frequency doubling perimeter and multifocal VEP testing detected visual field abnormalities when the standard achromatic 24-2 test showed no defect. There was only modest agreement between frequency doubling perimeter and multifocal VEP results in eyes without defects in the reference 24-2 test (#2121). Another study found that an abnormal result in frequency doubling perimetry showed a high risk of a future scotoma on Humphrey visual field testing 3 years later, even if the original Humphrey visual field showed normal results (#2129).

EXTRAOCULAR MUSCLES/EYE MOVEMENTS

The extraocular muscles in adenine nucleotide translocator 1 mutant mice had the typical appearance of mitochondrial myopathy seen in chronic progressive external ophthalmoplegia (#5009). Latanoprost was no more effective than placebo in the management of benign essential blepharospasm (#259). Ice pack application in benign essential blepharospasm patients was associated with a 50% to 66% decrease in blink rate; by comparison, normal subjects and patients with Graves disease had a 10% or less reduction in blink rate (#260). Botulinum toxin (Botox, Allergan Inc., Irvine, CA) injections (8–10 injections of 50 units/ml in the upper eyelid above the superior border of the tarsus) in the management of active-phase Graves eyelid retraction caused 77% percent of the eyelids to return to normal position 1 to 2 mm below the limbus. Approximately half of the patients continued to receive injections every 3 months to maintain the effect. The most common complications were ptosis and lagophthalmos (#263).
ORBIT

In a series of 1,264 patients with orbital masses, 64% were benign and 36% malignant, with the percentage of malignant tumors increasing with age (#4693). A comparison of exophthalmometry readings in 39 normal Asian and 69 normal white adults found significantly lower values in Asians (#48). In a Japanese study, the degree of proptosis correlated well with the severity of ocular manifestations of dysthyroid ophthalmopathy (#2717). However, another study showed that higher exophthalmometry readings did not correlate with a higher incidence of compressive optic neuropathy (#1610). In an attempt to measure the orbital volume deficiency after enucleation, investigators used perforated swimming goggles in 15 patients after enucleation. The difference in the amount of water that could be placed into the goggle-bounded cavity was used to assess the amount of volume replacement in dermis–fat grafting (#34). A study of the factors that predicted the need for adjuvant radiation therapy after corticosteroid therapy in sclerosing orbital pseudotumor in eight biopsy-proven cases found that neither age nor gender predicted the need for adjuvant radiotherapy (#269).

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There were 1344 scientific papers and poster presentations at the 56th Annual Meeting of the American Academy of Neurology held in San Francisco from April 24 to 30, 2004. The scientific abstracts may be found in Neurology (2004;62[Suppl 5]). We have summarized the material most interesting to neuro-ophtalmologists.

OPTIC NEURITIS/MULTIPLE SCLEROSIS

A double-blind, randomized, placebo-controlled study of intravenous immunoglobulin (IVIG) administered within 30 days of onset of optic neuritis (ON) enrolled 68 patients and studied contrast sensitivity, visual acuity, color vision, visual evoked potential, magnetic resonance imaging (MRI), and relapse rate at 6 months. There was no difference between the two groups in visual parameters at 7 days, 30 days, or 6 months. The authors appropriately concluded that IVIG does not affect the course or outcome of acute ON, although the time to recovery was not reported (Roed HG, Hvidovre, Denmark, S29.005).

A study of IVIG in relapsing–remitting multiple sclerosis (MS) was performed in patients whose visual acuities were worse than 20/200 at 60 to 90 days after an episode of ON, despite an initial course of pulsed intravenous methylprednisolone. Patients examined within 3 months of ON onset were treated with IVIG at 400 mg/kg per day for 5 consecutive days, followed by monthly IVIG at the same dose for five additional monthly infusions while continuing previous immune therapy. Patients examined after 3 months after ON onset were followed clinically while maintaining previous therapy. Six months after onset of IVIG therapy, 21 of 23 patients improved in visual acuity to 20/30 or better. In five patients, visual evoked potential also showed reversal of previous delayed conduction. In the untreated group, only 3 of 24 patients improved in visual acuity to 20/70 or better. In six patients, visual evoked potential repeated more than 6 months after onset showed no significant improvement in P100 latencies. Although this study suggests that IVIG may help refractory ON, the results must be interpreted in the context of a nonrandomized, open-label study (Khan O, Detroit, Michigan, P02.121).

For patients with ON and other clinically isolated demyelinating syndromes, the brain MRI is known to be a predictor of the development of future neurologic events consistent with MS. Although brain atrophy was not evident by MRI at baseline among patients in the Controlled High-Risk Avonex MS Prevention Study (CHAMPS), follow-up analyses of treated (interferon B-1a) and placebo patients have demonstrated that brain atrophy does develop within 5 years after first demyelinating events (including ON). The median baseline brain parenchymal fraction (BPF, brain volume/[brain + cerebrospinal fluid volume]) in CHAMPS was 0.857. BPF decreased by 1.146% between the 6-month and 5-year follow-up assessments. Although this rate of change is significant, it is less than that reported previously in cohorts of patients with relapsing–remitting MS in phase III clinical trials, suggesting a potential benefit of early immunomodulatory therapy in reducing the development of brain atrophy, which is an imaging marker for axonal/neuronal loss. Baseline T2 lesion volume was an independent predictor of decline in BPF, emphasizing the value of early MRI findings in determining prognosis (Kinkel R, Boston, Massachusetts, S46.002).

The risk of progressing to MS was described for a prospective cohort of patients with ON recruited in 1969 to 1981 (before MRI) and followed-up for up to 31 years or until MS was diagnosed. MRI, cerebrospinal fluid examination, and HLA typing were performed. The estimated 15-year risk of MS was 40% (confidence interval [CI]: 31%-52%). In most cases (60%), MS developed within 3 years. Among factors present at onset, inflammatory cerebral spinal fluid findings significantly increased the risk ($P = 0.02$) from 23% (CI: 12%-44%) to 49% (CI: 38%-65%). Recurrence of ON similarly elevated the risk significantly ($P < 0.001$). Younger patients and those with winter onset had greater risk. The presence of HLA DR2 did not increase the risk significantly. After 19 to 31 years, two or more MRI lesions suggestive of demyelinating disease were detected in 20 of 30 individuals in whom no clinical manifestations of MS had occurred. Although the authors point out that the 15-year risk of MS in this cohort was only 40%, this study was initiated in the pre-MRI era, when diagnoses of AION and neuroretinitis were not common. These cases may therefore have accounted for a substantial proportion of patients purported to have ON. Inclusion of these patients may, therefore, have artificially decreased the reported rate of conversion to MS (Sandberg-Wollheim M, Lund, Sweden, S40.003).

CHAMPS was a randomized, double-blind, placebo-controlled trial of interferon beta (IFNb)-1a 30 µg intramuscularly once weekly in patients who experienced a first
clinical demyelinating event. Results showed that IFNb-1a significantly slowed the rate of development of clinically definite MS (CDMS) and new MRI abnormalities over 2 years compared with placebo. The study was continued as an open-label extension study (CHAMPIONS). CHAMPIONS patients were offered intramuscular IFNb-1a for up to 5 years (timed from randomization into CHAMPIONS) and were followed-up every 6 months. Patients who received placebo in CHAMPIONS were considered the delayed treatment (DT) group and patients who received IFNb-1a in CHAMPIONS were considered the immediate treatment (IT) group. Outcomes included rate of development of CDMS, relapses, measures of disability, and MRI measures. Seventy percent (203/290) of patients from 32 participating sites were enrolled in CHAMPIONS (n = 100, IT group; n = 103, DT group). Overall, 36% of the IT group and 48% of the DT group had CDMS by 5 years. Mean number of relapses over 5 years (±SD) was 0.9 (±1.3) in the IT group compared with 1.7 (±2.7) in the DT group (P = 0.003), representing a 47% reduction in the IT group. In both groups combined, 13% of patients had an Expanded Disability Status Scale score of 3.0 or more at their 5-year visit (IT group 11%, DT group 14%). The median number of new or enlarging T2 lesions at 5 years was significantly lower in the IT group than in the DT group (3.5 vs. 6.0, P = 0.05). Initiation of IM IFNb-1a at the time of a first clinical demyelinating event slowed the rate of conversion to CDMS over 5 years compared with therapy initiated a median of 2.5 years later. These results support the recommendation to initiate disease-modifying therapy in high-risk patients at the time of a first demyelinating event (Kinkel RP, Boston, Massachusetts, S29.006).

To assess the bioavailability of oral high-dose prednisone, 16 MS patients were randomized to receive 1 g intravenous methylprednisolone (IVMP) or 1,250 mg of oral prednisone. Serum prednisolone and methylprednisolone levels were determined at 0, 1, 2, 4, 8, 24, and 48 hours after the first dose. There was no statistically significant difference in corticosteroid serum levels at 24 or 48 hours, but there was at 8 hours, consistent with an earlier peak in the intravenous group. This small study suggests that there is no substantial difference in the bioavailability of methylprednisolone and prednisolone at 24 hours after intravenous or oral dosing. Results are consistent with previous studies that have shown no differences in visual outcome but indicated reasonable tolerability for high-dose oral steroids as an alternative to IVMP (Morrow SA, London, Ontario, Canada, P02.117).

A 5-year study to determine whether regular pulses of IVMP affect the evolution of T2 lesions into confluent T2 lesions was undertaken. Eighty-eight relapsing–remitting MS patients were randomly assigned to regular pulses of IVMP (1 g/d for 5 days with an oral prednisone taper) or IVMP at the same dose schedule administered only for relapses. The patients were not treated with other disease-modifying drugs. Confluent T2 lesions were defined as lesions larger than 20 mm in strategically important areas of the brain or areas of white matter abnormalities consisting of two or more than two interconnected T2 lesions. Patients who received TVMP pulses every 4 to 6 months for 5 years had significantly fewer confluent T2 lesions (105 versus 270, P < 0.0001) and fewer large T2 lesions (>10 mm) (165 vs. 541, P < 0.00001) compared with those who received IVMP for relapses alone (Zivadinov R, Buffalo, New York, P04.035).

To evaluate the effects of neutralizing antibodies (NAbs) on the clinical efficacy of IFNb during treatment of MS, an open-label study of 78 patients prescribed any of the three main IFNb medications were studied. Of 78 patients enrolled in the study, 13 (17%) had persistent NAbs. The incidence of persistent NAb-positive patients was 35% for IFNb-1b, 20% for IFNb-1a-Rebif, and 3% for IFNb-1a-Avonex. NAb+ and NAb− patients showed reductions from baseline in relapse rate over the 3-year follow-up period. However, this reduction was not significant in NAb+ patients (25%, P = 0.053) but was highly significant (67%; P < 0.0001) in NAb− patients. In addition, the mean relapse rate was significantly higher (P = 0.039) and the mean time between first and second relapse was significantly shorter (13 vs. 21 months; P = 0.0064) in NAb+ compared with NAb− patients. The probability of being relapse-free was significantly lower (P = 0.08) in NAb+ than in NAb− patients. A significantly higher percentage of NAb+ patients had worsening of Expanded Disability Status Scale scores during follow-up (P = 0.013). Results of this study, funded by various health foundations, indicate that NAb testing should be considered in patients with continued relapses or progression despite therapy with IFNb (Malucchi S, Torino, Italy, P02.125).

Apo E is involved in the transport of lipids necessary for membrane repair in neuronal cells. Carriage of the Apo E4 allele has been associated with unfavorable outcomes in head trauma and stroke and is considered a risk factor for early-onset Alzheimer disease. The relation of Apo E4 to MS, an open-label study of 78 patients prescribed any of the three main IFNb medications were studied. Of 78 patients enrolled in the study, 13 (17%) had persistent NAbs. The incidence of persistent NAb-positive patients was 35% for IFNb-1b, 20% for IFNb-1a-Rebif, and 3% for IFNb-1a-Avonex. NAb+ and NAb− patients showed reductions from baseline in relapse rate over the 3-year follow-up period. However, this reduction was not significant in NAb+ patients (25%, P = 0.053) but was highly significant (67%; P < 0.0001) in NAb− patients. In addition, the mean relapse rate was significantly higher (P = 0.039) and the mean time between first and second relapse was significantly shorter (13 vs. 21 months; P = 0.0064) in NAb+ compared with NAb− patients. The probability of being relapse-free was significantly lower (P = 0.08) in NAb+ than in NAb− patients. A significantly higher percentage of NAb+ patients had worsening of Expanded Disability Status Scale scores during follow-up (P = 0.013). Results of this study, funded by various health foundations, indicate that NAb testing should be considered in patients with continued relapses or progression despite therapy with IFNb (Malucchi S, Torino, Italy, P02.125).
patients with ON and MS (Laustrup J, Copenhagen, Denmark, P06.070).

Balance dysfunction secondary to involvement of the brainstem vestibular pathways is a common manifestation of MS. Forty-four patients who completed an 8-week specialized vestibulo-ocular retraining program (consisting of repetitive practice of vestibular ocular reflex and visual exercise) demonstrated significant improvement in walking tasks as assessed by the Dynamic Gait Index as compared with a control group (n = 35) that completed an 8-week program of therapeutic exercise without specific balance re-training. Because patients who completed the specialized training demonstrated improvement compared with control subjects, results of this study suggest that systematic programs of vestibular rehabilitation are effective not only in patients with peripheral vestibular dysfunction but also in patients with MS and other disorders of the brainstem vestibular pathways (Bennett S, Buffalo, New York, P06.007).

**NEUROMYELITIS OPTICA**

Neuromyelitis optica (NMO) is an inflammatory demyelinating disease characterized by selective involvement of the optic nerves and spinal cord. A recent analysis comparing cerebral spinal fluid immunologic markers in NMO patients, MS patients, and healthy controls provided further evidence that a major humoral immune response occurs in the cerebral spinal fluid of patients with NMO. Production of anti-myelin oligodendrocyte glycoprotein IgM and activation of eosinophils were factors more associated with NMO than MS or control subjects. The potential role for these findings in the pathogenesis of NMO remains to be investigated (Correale J, Buenos Aires, Argentina, P05.048; Battisti C, Siena, Italy, POL 103). Based on a model of apoptotic cell death in LHON, novel mutations are frequently sought in sporadic cases and in familial cases in which known mutations are not identified. Novel, rare pathogenic mutations have been reported within the ND6 subunit of the mitochondrial genome, now a mtDNA point mutation (3733G>A transition) that induces an E143K amino acid change within the ND1 subunit gene has been discovered. In these analyses, a 3733G>A nucleotide change was identified in one sporadic case of LHON and in a family with six maternally related affected individuals. All of these patients were negative for known LHON mutations. Findings from this investigation provide evidence that the ND1 subunit represents a second "hot spot" (in addition to ND6) for mtDNA mutations in patients and families with LHON that may be targeted for genetic testing (Valentino M, Bologna, Italy, P01.101).

Investigation of the processes by which mutations in mtDNA lead to apoptotic cell death in LHON is important in demonstrating potential targets for neuroprotective therapies. Two groups in Italy recently showed that LHON mutations profoundly impair ATP synthesis in mitochondria (Carelli V, Bologna, Italy, P01.102), and that the apoptotic process induced by oxidative stress primarily involves alterations in mitochondrial membrane permeability (Battisti C, Siena, Italy, P01.103). Based on a model of apoptosis using cells cultured in galactose-containing rather than glucose-containing medium (cells with mtDNA mutations at positions 11785, 3460, and 14484), Carelli et al demonstrated that impairment of ATP synthesis may be more relevant than previously thought in the process of retinal ganglion cell death. In peripheral blood lymphocytes from six patients with LHON, Battisti et al investigated the potential role of 2-deoxy-d-ribose (a factor that alters redox
homeostasis) on the apoptotic response. The rationale for this study was based on the fact that, given the incomplete penetrance of the LHON phenotype (optic neuropathy develops in only 10% of women and 50% of men with the three most common mutations), additional genetic or environmental factors (such as oxidative stress affecting mitochondrial function) are likely to be important modifiers of phenotype expression. Based on these investigations, agents that reverse or prevent effects of oxidative stress or that enhance ATP synthesis represent potential therapeutic strategies for preventing cell death in LHON and other mitochondrial disorders. The feasibility and timing of such future therapies remain to be established.

A retrospective review of 100 cases of optic nerve hypoplasia (ONH) studied the frequency of coexisting neurologic and endocrine abnormalities. There were 64 men and 36 women, 75% with bilateral ONH, 21% with premature birth, 9% with fetal alcohol syndrome, and 7% with maternal diabetes. All patients had impaired vision or strabismus. There was a clinical neurologic abnormality in 57% of bilateral ONH patients and 32% of unilateral ONH patients and endocrine abnormalities in 6% of all patients combined. Developmental delay was present in 32%, cerebral palsy in 13%, and seizures in 12%. Of 65 patients with imaging studies, 60% had abnormalities, including 25% with dysplasia of the ventricles or white or gray matter, 16% with dysplasia of the corpus callosum, 10% with septo-optic dysplasia, and 8% with hydrocephalus (Rothner AD, Cleveland, Ohio, P01.125).

**MIGRAINE**

Vestibular dysfunction is now recognized as a frequent cause of symptoms in patients with migraine. Documentation of clinical findings in these patients, however, has been largely limited to asymptomatic periods between migraine episodes, making the diagnosis of vestibular migraine one of exclusion. A recent series of 26 patients, examined during or immediately after an acute attack, demonstrated the occurrence of nystagmus in the setting of acute or subacute vestibular migraine. Although clinical descriptions of the nystagmus were variable, eye movement recordings showed consistent patterns suggesting a central origin that were readily distinguishable from benign paroxysmal positional vertigo. Same-day examination of patients with recurrent intermittent positional vertigo is a useful strategy for diagnosis (Hartman S, Atlanta, Georgia, 503.001).

Some insights into the mechanism of prolonged migraine aura were gained from a study of two patients who had a 1-week aura. The first patient had Sturge-Weber syndrome in addition to migraine and presented with prolonged aura of left homonymous hemianopia lasting 1 week. Neuroimaging studies during the aura showed focal hyperemia in the right occipital cortex on single photon emission computed tomography, augmented gadolinium leakage from the leptomeningeal angiomatosis along the sulci of the right occipital cortex on enhanced MRI, and retention of the contrast material in the leptomeningeal vessels of the right medial occipital cortex on CT angiography. The neuroimaging findings resolved with the clinical symptoms. The second patient, who had hemiplegic migraine presenting with right hemiparesis, confusion, and global aphasia as a prolonged aura, underwent neuroimaging studies that showed widespread hyperemia in the left cerebral hemisphere on single photon emission computed tomography, vasodilatation of the left middle cerebral artery on MRA, and gadolinium enhancement of the cerebral spinal fluid in the sulci of the left parieto-occipito-temporal cortex on delayed enhanced fluid-attenuated inversion recovery images obtained 2 hours after gadolinium administration. The authors suggest that vasogenic leakage from the leptomeningeal vessels, possibly associated with trigeminovascular activation, may delay the process of spontaneous recovery or prolong the state of neuronal suppression in patients with prolonged migraine aura (Izuka T, Sagamihara, Japan, P01.152).

**IDIOPATHIC INTRACRANIAL HYPERTENSION**

A retrospective study of 77 idiopathic intracranial hypertension (IIH) patients in Detroit found that 92% were female, 88% were obese, 65% were black, and 31% were white. The most common presentation was isolated headache (28.6%); 24.7% of patients were asymptomatic (Van Stavern GP, Detroit, Michigan, P01.098).

The features of 20 IIH patients without papilledema (6% of a total of 353 patients) were compared with the other 94% who did have papilledema. Eighteen were women, 84% were overweight, and 90% had headaches. When compared with those with papilledema, the patients without papilledema had fewer transient visual obscurations, intracranial noises, and diplopia. Visual acuity was similar in both groups. Automated visual field tests showed similar mean deviations in both groups, but there were more psychogenic visual field defects in those without papilledema. Opening pressures tended to be lower in IIH without papilledema (312 mmH₂O vs. 373 mmH₂O, P < 0.01) (Nakamoto BK, Salt Lake City, Utah, P01.099).

Nine patients with severe rapid visual loss from IIH ("malignant IIH") were presented. All were women with a mean age of 23 years. Six were obese, and none was anemic. All had had acute, severe headaches as an initial symptom, prompting rapid evaluation and diagnosis of papilledema from raised ICP. Visual acuity was 20/200 or worse in at least one eye at initial presentation. All had severe, bilaterally constricted visual fields and bilateral disc edema. All patients underwent at least one lumbar puncture and were
treated with acetazolamide (1,000 to 2,000 g/day) early in the course with progressive worsening of visual function despite treatment. All underwent emergent optic nerve sheath fenestration (unilateral in four, bilateral in three) or lumbo-peritoneal shunting (five). Visual function improved in all patients but details were not given. The authors conclude that medical management alone may be inadequate and that prompt surgical intervention may be indicated to preserve vision (Thambisetty M, Atlanta, Georgia, PO1.100).

In advance of an IIH treatment trial, baseline and 6-month follow-up information was collected on 109 patients with newly diagnosed IIH at multiple centers. Median age at presentation was 30 years (range 13–52 years). 93% were women, 83% were white, and 13% were black. Symptoms were headache (44%), visual loss (29%), transient visual obscurations (10%), diplopia (4%), or other (3%). Forty-two eyes (19%) had visual acuity worse than 20/25 at baseline and 24 eyes (11%) had visual acuity worse than 20/25 at follow-up. Abnormal visual fields were found in 67% of eyes at baseline and 50% of eyes at follow-up. The average Humphrey mean deviation at baseline was −3.11 dB OD and −3.03 dB OS. At follow-up, the average mean deviation was significantly improved at −2.18 dB OD and −3.03 dB OS. At follow-up, the average mean deviation was significantly improved at −2.18 dB OD and −3.03 dB OS. There was a high correlation between the mean deviation at baseline and at follow-up (Pearson r = 0.85 for OD and r = 0.78 for OS) (Friedman, DI, Rochester, New York, PO1.097).

CEREBROVASCULAR DISORDERS

A report compared 290 patients with unruptured intracranial arteriovenous malformation (AVM) treated with surgery, embolization, or radiation to 108 patients with AVM that was not treated. Incomplete AVM treatment increased the risk of symptomatic hemorrhage and acute clinical worsening compared with no treatment. Complete lesion removal resulted in a 5-year risk of bleeding equivalent to that of untreated patients. The authors rightfully suggest that their findings support the need for a randomized trial for treatment of unruptured brain AVMs (Mohr JP, New York, New York, SI3.003).

Traditional teaching is that dolichoectatic aneurysms caused by atherosclerosis are not associated with subarachnoid hemorrhage. In a review gathered from the experience of five major hospitals in a recent 5-year period, six elderly patients were identified with subarachnoid hemorrhage caused by rupture of dolichoectatic basilar artery aneurysms. Symptoms of aneurysm growth or clot formation within the dolichoectasia (because of compression or brainstem ischemia) preceded its rupture in most cases and the outcome was invariably fatal (Michel P, Utrecht, The Netherlands, SI3.004).

To further clarify the relationship of headache and stroke, a prospective cohort study of 39,754 women health professionals participating in the Women’s Health Study was performed. Migraine, aura symptoms, and headache were accepted as self-reported, but incidence of self-reported ischemic and hemorrhagic stroke was confirmed after medical record review. During an average of 9 years of follow-up, 385 strokes (309 ischemic, 72 hemorrhagic, and 4 undefined) occurred. Compared with non-migraineurs, participants who reported migraine without aura had no increased risk for ischemic or hemorrhagic stroke. Those who reported migraine with aura had a significant increase in risk for stroke, with an adjusted hazards ratio (HR) of 1.53 (95% confidence interval [CI]: 1.01–2.30) for the hemorrhagic and ischemic stroke combined and 1.70 (95% CI: 1.10–2.64) for ischemic stroke alone. Participants who were younger than age 55 years had the greatest increased risk of total (HR 1.74; 95% CI: 1.01–3.00) and ischemic (HR 2.25; 95% CI: 1.30–3.90) stroke. There was no increase in the risk of hemorrhagic stroke among migraineurs. Compared with participants without a reported history of any headache, non-migraine headache was not associated with an increased risk of hemorrhagic and ischemic stroke combined (HR 0.99; 95% CI: 0.73–1.33), ischemic stroke alone (HR 0.91; 95% CI: 0.64–1.28), or hemorrhagic stroke alone (HR 1.27; 95% CI: 0.67–2.40). It appears that migraine with aura is associated with an increase in hemorrhagic and ischemic stroke combined and ischemic stroke alone, particularly among young women. Migraine without aura and non-migraine headache are not associated with increased risk of stroke. Migraine with aura was not associated with an increased risk of hemorrhagic stroke (Kurth T, Germany, S24.001).

To determine the accuracy of CT angiography for evaluation of carotid stenosis compared with conventional digital subtraction angiography (DSA), two masked readers retrospectively evaluated 81 arteries in consecutive TIA and stroke patients who had undergone both studies over a 32-month period. Using a 70% stenosis cut-off value, CTA and DSA were in agreement in 78/81 (96.3%) of vessels. The negative predictive value of a CTA demonstrating less than 70% stenosis was 100%. Three of 81 (3.7%) vessels evaluated by CTA as greater than 70% were found to be less than 70% by DSA. One vessel was overcalled by CTA secondary to calcification. The authors appropriately suggest that CTA is a valid screening tool for significant carotid stenosis and can be used in the initial evaluation of stroke (Josephson SA, San Francisco, California, S16.003).

In North Carolina, a survey of stroke mortality rates at all 128 hospitals showed that care in a basic or advanced stroke center significantly decreased mortality (Camilo O, Durham, North Carolina, PO3.074).
To assess whether retinal vascular disease consisting of arteriosclerosis, exudates, or hemorrhages was associated with subsequent myocardial infarction or stroke, 20-year follow-up data of 4,753 adults aged 25 to 74 years who participated in the First National Health and Nutrition Examination Survey (NHANES) was reported. Of the 4753 participants, 935 (20%) had baseline retinal vascular disease on funduscopic examination. At an average of 16.1 years of follow-up, the rate of cardiovascular diseases was 35% in patients with retinal vascular disease and 18% in patients without retinal vascular disease. After adjusting for differences in age, race, sex, systolic blood pressure, smoking habit, serum cholesterol levels, body mass index, and diabetes mellitus, the risk of all cardiovascular diseases was increased in persons with retinal vascular disease (relative risk [RR], 1.2; 95% CI: 1.0-1.3). The age-adjusted and sex-adjusted risk of myocardial infarction (RR 1.1; 95% CI: 1.0-1.4) and ischemic stroke (RR 1.3; 95% CI: 1.0-1.6) was higher among persons with retinal vascular disease (Qureshi A, Newark, NJ, P03.131).

A retrospective, multicenter study of 90 consecutive cases with isolated Horner syndrome from internal carotid artery dissection was undertaken, with a median follow-up of 2 years. Horner syndrome was painless in 8 and painful in 82 patients. After onset of Horner syndrome, the 2-year risk of transient ischemic attack and stroke was 17%, and the risk of stroke alone was 12%. Eleven middle cerebral artery strokes occurred, 10 within the first 15 days and 36% within the first 24 hours. Five patients with stroke had DSA, all demonstrating fibromuscular dysplasia (de Bray JM, Zurich, Switzerland, P03.137).

SPORTIF V was a double-blind trial of 3922 patients with non-valvular AF and at least one stroke risk factor who were randomized to treatment with fixed-dose oral ximelagatran (36 mg twice daily) or adjusted-dose warfarin (target INR 2.0-3.0). The primary endpoints were stroke and systemic emboli. Fixed-dose, oral ximelagatran without coagulation monitoring was found to be at least as effective as warfarin in prevention of stroke and systemic emboli, and was associated with less bleeding, confirming the results of the earlier open-label SPORTIF III trial. This might improve the compliance and ability to anticoagulate patients because INR does not have to be followed (Albers GW, Palo Alto, California, PL03.131).

VENOUS SINUS THROMBOSIS

Patients with venous sinus thrombosis generally undergo extensive evaluation for hypercoagulable factors. A recent case series revealed that elevated levels of yet another prothrombotic factor, lipoprotein (a) [Lp(a)], may be associated with venous sinus thrombosis. Lp(a) is an inherited prothrombotic lipid fraction and has been demonstrated in patients with accelerated atherosclerosis and venous thromboembolism. Elevated levels of Lp(a) were noted in 9 of 15 patients with non-obstructive (non-compressive) venous sinus thrombosis, but five of these patients also had coexistent hypercoagulable disorders, including antiphospholipid antibodies, anti-β(2)-glycoprotein-I antibodies, and heterozygosity for the factor V Leiden mutation. These results provide some evidence, however, that measurement of Lp(a) level should be added to the hypercoagulable assessment in patients with venous sinus thrombosis and other thrombo-embolic disorders. Further investigation of this prothrombotic lipoprotein may reveal a potential role for therapy with agents used to treat hyperlipidemia (Liebeskind D, Philadelphia, Pennsylvania, P06.027).

A case-control study of 45 Mexican patients with cerebral venous thrombosis and 90 control subjects measured plasma levels of homocysteine (fasting and after methionine load), folate, and vitamin B12. Genotyping of the methylene tetrahydrofolate reductase (MTHFR) gene was also performed. High plasma concentrations of homocysteine and low plasma folate levels were associated with an increased risk of cerebral venous thrombosis in this population whose low socioeconomic status and deficient nutrition may be contributory. Although there was a higher incidence of MTHFR mutation in cerebral venous thrombosis patients (22% vs. 10%), the difference did not reach statistical significance (Cantu C, Mexico, P01.052).

HEADACHE

Chronic cluster headache (CCH) is the most severe form of chronic headache. Positron emission tomography studies have shown posterior hypothalamic hypermetabolism during attacks. Two studies of hypothalamic stimulation for intractable CCH were presented. In the first study, 14 CCH patients (12 men, 2 women, mean age 41.4 years, range 25–63 years), received hypothalamic stimulation. At a mean follow-up of 15 months, nine patients were pain-free, and three others had more than 80% reduction in attacks. In one patient, the stimulator was switched off eight times and the mean time of return of headache to pain-free state was 7.6 days (range 2–29 days). The authors concluded that continuous stimulation of the postero-inferior hypothalamus is an effective, safe, and well-tolerated treatment of intractable CCH (Leone M, Milano, Italy, S43.001). A second study of hypothalamic stimulation for CCH included five patients (four men). Four of five patients experienced major improvement, which persisted after a mean follow-up of 8 months. One patient remained attack-free, one experienced two brief relapses that could be controlled by increasing stimulation parameters, and one still presented some scattered attacks, but frequency was reduced by 85%. In the latter two CCH patients, remaining attacks were well-controlled by oxygen or sumatriptan and none required drug prophylaxis. The fifth patient had a fatal...
intracranial hemorrhage 4 hours after the surgical electrode implantation, a reminder that this intervention is not entirely benign (Vandenheede M, Liege, Belgium, S43.002).

Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) syndrome is a rare, usually drug-refractory headache. Pain attacks occur hundreds of times per day, last a few seconds, are experienced along the first branch of the trigeminal nerve, and are accompanied by autonomic phenomena such as lacrimation, eye reddening, rhinorrhea, nasal stuffiness, and facial flushing. Based on similarities to cluster headaches and a previous report of functional MRI demonstrating ipsilateral hypothalamic activation, a patient with SUNCT received ipsilateral hypothalamic deep brain stimulation. Pain attacks gradually decreased. Four months after implantation, the patient was pain-free (Leone M, Padova, Italy, S43.003).

An open-label trial of botulinum-A toxin in the treatment of trigeminal neuralgia, idiopathic stabbing headaches, and SUNCT was presented. Three of seven patients with trigeminal neuralgia became pain-free after 15 days, two had an 85% reduction of symptoms, and two did not improve at all. Three of four patients with idiopathic stabbing headaches were pain-free 15 days after the injections. At the 3-month follow-up, one had pain recurrence at another site. The single SUNCT patient reported worsening in the three first postinjection days, with a 70% reduction of symptoms after 21 days (Piovesan EJ, Parana, Brazil, P02.105). Results of this study suggest that botulinum toxin may be effective in the symptomatic treatment of some headache syndromes.

There have been previous reports of SUNCT secondary to an underlying lesion, mostly in the posterior fossa. A 69-year-old woman who had 50 to 70 lancinating right orbital pain attacks per day lasting 1 to 2 minutes would sometimes have conjunctival injection, profuse ipsilateral lacrimation, ptosis, rhinorrhea, and eyelid edema. Neurologic and ophthalmologic examination between attacks was normal. A gradually enlarging right orbital lesion was found. The symptoms then became contralateral and a left orbital lesion was found. Metastatic bronchial carcinoma was diagnosed, but biopsy was not performed on the orbital lesions (Black DF, Scottsdale, Arizona, p04.159).

MYASTHENIA GRAVIS

Although patients with ocular myasthenia gravis (OMG) do not experience the potentially life-threatening manifestations of bulbar and respiratory muscle weakness, diplopia and ptosis may be disabling. Systemic corticosteroids are known to produce clinical improvement in patients with generalized MG, but their efficacy as compared with pyridostigmine for treating OMG has not been established. A review of clinical data from 88 OMG patients who received oral prednusone (50–60 mg/d with gradual taper) or pyridostigmine (180 mg/d with dose escalation as tolerated) in a non-randomized fashion showed a significant benefit for corticosteroids in reducing diplopia and ptosis. The proportion of patients experiencing diplopia in primary gaze decreased within 1 month of treatment from 94.6% to 26.5% in the prednusone group; this effect was sustained for at least 2 years in 70% of patients. The pyridostigmine group, in contrast, manifested diplopia in primary gaze in 85.3% at baseline and in 93.1% at 1 month. Prednusone therapy also demonstrated reduced ptosis significantly more often than did pyridostigmine. Although patients in this study were not randomized to treatment groups, the results provide evidence in support of future randomized trials to examine tolerability and efficacy of corticosteroids in patients with OMG. The potential for corticosteroids to delay or prevent the onset of generalized MG in OMG patients will also be investigated in upcoming trials (Kupersmith M, New York, New York, S03.004).

In contrast to previous reports, a Japanese study found that only 9 (26%) of 35 acetylcholine receptor antibody (AChRAB)-negative MG patients to be musclespecific tyrosine kinase (MuSK) Ab-positive. MuSK is a surface membrane enzyme that is essential in aggregating AChR during the development of the neuromuscular junction. All nine patients were women and symptoms were dysphagia, neck muscle weakness, and respiratory failure, with little ocular or limb muscle weakness. Four of these nine patients experienced myasthenic crisis and none had thymomas. Repetitive nerve stimulation showed mild decrement (from 0% to 17%) despite severe symptoms. MuSK Ab-positive patients had only mildly decreased AChR density and two of six had immune complex deposition at the motor end-plates, which was different than that of the MuSK Ab-positive patients. Based on these contrasts, the authors suggest that the pathogenesis of AChRAB-negative MG may be a different form of MG that AChRAB-positive MG (Shiraishi H, Nagasaki, Japan, S22.003).

Congenital myasthenic syndromes comprise a heterogeneous group of rare disorders arising from genetic defects in presynaptic, synaptic, or postsynaptic proteins at the neuromuscular junction. Most AChR-deficient patients have AChR-e subunit mutations, but recently mutations in the endplate AChR clustering protein, rapsyn, have been shown to be an additional cause, being associated with two distinct phenotypes: early-onset and late-onset. Twenty-eight early-onset AChR-deficient patients were described, 14 with AChR-e mutations and 14 with rapemy mutations. All had symptoms from birth or infancy. Ptosis, severe ophthalmoplegia, and generalized weakness were associated with AChR-e mutations. By contrast, mutated rapsyn patients did not have ophthalmoplegia but rather arthrogryposis multiplex congenita (n = 10), marked bulbar weakness.
INHERITED ATAXIAS

Mutations in CACNA1A, the gene encoding the human P/Q-type voltage-gated calcium channel alpha 1A subunit, cause episodic ataxia type 2 with interictal nystagmus and other symptoms including hemiplegic migraine, progressive ataxia, epilepsy, and fluctuating weakness. A novel type of episodic ataxia type 2 causing CACNA1A mutations affecting the splice donor site at intervening sequence +3 was described (Jen JC, Los Angeles, California, POL 106).

Three cases were reported of ataxia-ocular apraxia 2 (AOA2), a new autosomal recessive ataxia linked to a gene localized to 9q34 and encoding for a protein called senataxin. The disease presented with progressive ataxia and areflexia between ages 16 and 19 and, in one patient, ocular motor apraxia. Alpha-feto protein was elevated, electromyography showed an axonal neuropathy, and MRI revealed cerebellar atrophy (Fleury M, Strasbourg, France, P01.014).

In another series, AOA1 and AOA2 accounted for 5% to 10% of 154 patients (77 families) with non-Friedreich autosomal recessive cerebellar ataxia. There were five different truncating/missense mutations in AOA1, and four missense mutations in AOA2. AOA1 was characterized by an early mean age of onset (6.8 ± 4.3 years), less frequent chorea (44%), and less severe neuropathy. Biological markers, as well as oculographic patterns, were useful to distinguish these overlapping phenotypes. Although ocular motor apraxia is a common feature of both disorders, differences in the age at onset, as well as the frequency and severity of associated signs and biologic features, allow distinction between AOA1 and AOA2 (Durr A, Illkirch, France, P01.061).

A genotype-phenotype correlation of 100 cases of spinocerebellar atrophy (SCA) in Brazilian families was reported. Sixty-five percent had identifiable mutations. Two groups with neuro-ophthalmologic findings were reported. All SCA 2 patients (8% of total) had cerebellar ataxia with slow saccades and hyporeflexia in upper limbs; all cases of SCA 7 (5% of total) had cerebellar ataxia and decreased visual acuity (Teive GH, San Paolo, Brazil, P01.020).

A study comparing SCA2 patients to those with SCA6 and episodic ataxia type 2 was performed. Although all these patients have a similar type of ataxia, only SCA2 patients have slow saccades. This finding was correlated with significant atrophy of the pons in SCA2. All three groups had atrophy of the cerebellar flocculus (Ying SH, Los Angeles, California, P01.106).

The visual and oculomotor features of 14 patients with late-onset Tay-Sachs disease were described. There were eight men and six women between 24 and 53 years of age. Afferent visual function and funduscope examination was normal. Most often there was saccadic hypometria, although hypermetria sometimes occurred. Saccades also showed prolonged duration and decreased peak velocity. Large saccades showed "discrete decelerations," during which eye velocity had transient decreases. Slowing of saccades was present both horizontally and vertically, but was usually not conspicuous during bedside examination. There was decreased horizontal and vertical smooth pursuit gain. Vestibular ocular reflex and vergence movements were preserved and there was no nystagmus (Rucker JC, Cleveland Ohio, P01.105).

DEGENERATIVE DISEASES

Two patients presented with a focal tumor-like MRI lesion whose biopsy result was typical for Alzheimer disease. Their subsequent clinical course was also consistent with Alzheimer disease (Strand NH, Scottsdale, Arizona, P04.066).

A study of retinal nerve fiber layer thickness by optical coherence tomography in Parkinson disease (PD) was reported. Retinal nerve fiber layer thickness was significantly thinner in the inferior retinal quadrant of PD patients (146.6 ± 19.7 μm) than in controls (165.1 ± 15.7 μm, P = 0.032). Within the inferior quadrant, the infero-temporal part was the thinnest as compared with controls (P = 0.01),
Neuro-Ophthalmology at Large

The physiologic basis for "freezing" episodes in some patients with PD is not well understood. A study recently demonstrated that abnormalities of visual contrast sensitivity may contribute to the phenomenon of freezing, and that a relative hypersensitivity to low spatial frequency visual stimuli in the everyday visual environment may represent an important factor. Alternatively, findings of abnormal visual contrast sensitivity at low spatial frequencies and marked gait freezing may represent end-stage signs of dopamine deficiency in the visual and other central nervous system pathways in patients with Parkinson disease (Kraakevik JA, IA City, Iowa, P04.150).

Progressive ataxia with palatal myoclonus is a recently described clinical syndrome. The first pathologic case was presented and showed the expected olivary hypertrophy but also accumulation of intracytoplasmic tau in the dentate-rubral system, sparing the rest of the brain. This may be related to other degenerative "tauopathies." These are patients without previous stroke or radiation to the brainstem (Zoltan M, Bethesda, Maryland, P01.062).

**OCULAR MOTOR DISORDERS**

Saccadic adaptation refers to the ability to modify the amplitude of a saccade in the midst of performing that saccade. It may be tested by having a target move to a new location in the middle of a saccade. This paradigm was used to test if children had this ability, a function of a mature brainstem (Zoltan M, Bethesda, Maryland, P01.062). The same group reported that children had this ability, a function of a mature brainstem (Zoltan M, Bethesda, Maryland, P01.062).

The pathogenicity of tRNAser mitochondrial DNA mutations is generally low, usually resulting in relatively mild neurologic dysfunction (ataxia, dysarthria). A family with more severe findings related to this mutation and a mutation in A7472C was recently reported. Clinical features in a 72-year-old mother included a 20-year history of progressive imbalance in their early 70s. Three members of a family with autosomal dominant congenital facial palsy had a more than 20-year history of progressive weakness and deafness, whereas her 53-year-old daughter had exercise intolerance associated with progressive weakness, deafness, and stroke, whereas her 50-year-old son had a more than 20-year history of progressive weakness requiring the use of a motorized scooter. Thus, the phenotype of tRNAser may be influenced by other mutations in the mitochondrial genome (Haller RG, Dallas, Texas, P01.134).

A new, dominantly inherited audio-vestibular syndrome was described. Affected family members experienced slowly progressive hearing loss beginning in their late 30s and progressive imbalance in their early 70s. Three of four affected individuals had episodes of vertigo, typically lasting minutes and occurring several times per year. Auditory and vestibular function testing documented a slowly progressive loss of auditory and vestibular function. Postmortem examination showed a loss of hair cells in the cochlea and vestibular receptor organs (Ishiyama G, Los Angeles, California, P01.107).
MISCELLANEOUS

A personal account of sleep-related alterations associated with Wallenberg syndrome was given by a 67-year-old sleep physiologist and psychiatrist who had been a victim of this stroke. He described insomnia for the first 10 days after the stroke. Complex visual and vestibular hallucinations occurred on eye closure during the awake state. Commonly prescribed hypnotics (benzodiazepines, zolpidem, antihistamines) provided little relief, increased hallucinations, and led to a few dissociative episodes. Sleep progressively improved from day 10 to 40 after the stroke with slow resumption of dreaming (Silvestri RC, Boston, Massachusetts, P01.093).

In an attempt to determine whether an electroretinogram can be manipulated to simulate organic disease, five normal subjects were asked to be noncompliant while performing the test. Although abnormalities were noted, none simulated organic retinal disease (Reiss A, Atlanta, Georgia, P01.104).

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Neuro-Ophthalmology at the Mayo Clinic

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Six former Mayo Clinic physicians have contributed gloriously to the history of neuro-ophthalmology. Many have put their stamps—if not their names—on important medical conditions.

The Mayo Clinic tradition of neuro-ophthalmology dates back to the Mayo brothers themselves. Charles H. Mayo, MD, joined his father William W. Mayo, MD, and brother William (Will) J. Mayo, MD, in general practice in 1888 and set aside several hours per week to see patients with eye, ear, nose, and throat problems. Will Mayo attended the University of Michigan Medical School, one of the first medical schools to separate ophthalmology from the discipline of otolaryngology. While Will was a medical student, he had the chance to study anatomy and observe surgery with the University of Michigan ophthalmologists. On a return visit as an alumnus speaker in 1913, he learned that the University of Michigan had given the ophthalmology and otolaryngology departments separate wards to prevent contamination.

In 1915, Will Mayo helped implement a joint Mayo Clinic–University of Minnesota 3-year, university-based graduate school in medical specialties. The graduate physicians did clinical work and medical research and were granted the MS or PhD degrees in clinical specialties. Will organized separate sections of ophthalmology and otolaryngology but needed to replace Carl Fisher, MD, who practiced ophthalmology and otology, with a full-time ophthalmologist. William L. Benedict, MD, was selected to head the section of ophthalmology, which opened in 1917 and included Walter Ivan Lillie, MD, who became Mayo’s first neuro-ophthalmologist (Figs. 1 and 2).

Lillie had graduated from the University of Michigan Medical School in 1915, interned at the University Hospital in Ann Arbor, and practiced in Flint, Michigan, before arriving at the Mayo Clinic in 1917. Six weeks later, he was called to active duty in the United States Army, but in 1919 he returned to Mayo as an assistant in ophthalmology.

FIG. 1. Walter “Ivan” Lillie, MD. (Courtesy of H. Stanley Thompson, MD.)

FIG. 2. The 1914 Building photographed in 1924. Built in 1914 as the original Mayo Clinic building, it housed ophthalmology from 1917 to 1922. It was torn down in 1986. (Courtesy of the Mayo Archives.)
He did not register as a resident in the graduate school until 1920 when he became the seventh postgraduate resident in the ophthalmology department. He supplemented his ophthalmology training with assignments in the neurology department.

In 1921, Lillie joined Benedict and Avery D. Prangen, MD, on the ophthalmology staff at Mayo. At that time, the ophthalmology department was divided into three sections: surgery, strabismus/refraction, and the hospital consult service in medical ophthalmology. Lillie took over the hospital consult service from Prangen and concentrated on referrals from the neurology and neurosurgery services, which were primarily for visual field localization of lesions.

Lillie produced 20 publications, 16 on neuroophthalmic topics. One paper emphasized the usefulness of visual fields in localizing brain tumors, although he stated that “the actual occurrence of tumor of the brain is relatively rare” (1). He also wrote about optic neuritis and its recognition by other medical specialists (2). At that time, treatment consisted of pilocarpine sweats, intravenous typhoid or arsphenamine, or removal of infected teeth. In 1933, Lillie left the Mayo Clinic to become the chair of the ophthalmology department at Temple University. He died in Philadelphia while shoveling snow in 1947.

Henry P. Wagener, MD, (Fig. 3) received his undergraduate degree from Charleston College and his medical degree from the Medical College of South Carolina before coming to the Mayo Clinic as an ophthalmology resident in 1920. He joined the staff in 1926 and worked with Lillie on ophthalmology examinations requested by internal medicine or neurology at St. Mary's Hospital (Fig. 4).

Wagener published 100 articles and chapters, concentrating on the retinal vasculature in systemic disease (18 on the effects of hypertension on the eye). Along with internists Norman M. Keith, MD, and Nelson W. Barker, MD, he gained recognition for a classification of hypertensive retinopathy and related survival rates (3) at a time when hypertension therapy consisted solely of salt restriction and sympathectomy.

Wagener continued to work into the 1950s at St. Mary’s Hospital, performing visual fields on neurosurgery patients, often spending 6 hours on one visual field. A patient who had had repeated surgery for recurrence of a brain tumor and repeated visual fields performed by Wagener commented that he did not mind the brain surgery nearly as much as the visual field examinations. Wagener retired in 1955.

By the time Lillie left Mayo in 1934, ophthalmology had moved from the Zumbro Hotel Annex, where it had
moved in 1922, to the Plummer Building, where it remained until 1947 (Figs. 5 and 6). Hugo L. Bair, MD, replaced Lillie. Bair had received his undergraduate and medical degrees from Harvard, graduating from its medical school in 1929. After a 1-year internship and 21 months as an ophthalmology intern at the Massachusetts Eye and Ear Infirmary (MEEI), he spent 2 months at the MEEI’s Howe Laboratory serving as an ophthalmic research assistant.

At Mayo, Bair introduced the tangent screen. Residents were routinely assigned a rotation in perimetry early in their training and performed all the visual fields. When World War II began, there was a shortage of residents so the paramedical staff took over the performance of visual fields. During Bair’s tenure, ophthalmology moved to the Mayo Clinic Annex, where it remained until 1955 (Fig. 7).

Bair published 26 articles, six on topics in neuro-ophthalmology and four on dark adaptation. Aware of the impact of vitamin A on night vision, he tried to verify this by placing three subjects on a vitamin A-restricted diet (100–300 international units daily) for up to 190 days. None of the subjects had abnormal dark adaptation after this deprivation. Bair concluded that vitamin A intake can be deficient for quite some time without causing any physiologic changes in rod or cone sensitivity (4). He retired in 1969 (Fig. 8).

C. Wilber Rucker, MD, graduated from the University of Minnesota medical school in 1926 and was an ophthalmology resident at the Mayo Clinic from 1926 to 1929. He then returned to Minneapolis to practice ophthalmology and work in the student health service at the University of Minnesota while serving as an Instructor in Ophthalmology at the university’s medical school.

Joining the Mayo staff in 1934, Rucker was an active participant in morning lectures for the ophthalmology, neurology, and neurosurgery residents on the medical/neuro-ophthalmology service. Rucker once examined a chubby 11-year-old boy with retinitis pigmentosa. Correctly realizing that the boy had Bardet-Biedl syndrome, Rucker turned to the boy’s mother and asked rather quietly, “Does your son have six toes?” She remarked “My God, can you see down that far?”

Rucker was the first to write about retinal venous sheathing in patients with multiple sclerosis (5). Wagener had first observed retinal venous sheathing but believed that these changes were congenital. In 1947, Rucker submitted his thesis on 103 cases of venous sheathing in multiple sclerosis to the American Ophthalmological Society (AOS). Edward W. D. Norton, MD, later chair of ophthalmology at the Bascom Palmer Institute, University of Miami, read
that paper and was intrigued enough to spend a few months at Mayo after finishing his fellowship training. But during his 3-month stay, he did not see a single case of venous sheathing. On the day that he left for the airport, in walked a patient with that very condition. A squad was sent to the airport to retrieve Norton so that he could see the patient for himself. Frank B. Walsh, MD, later visited the Mayo Clinic to examine multiple sclerosis patients with venous sheathing.

Rucker served as chairperson of ophthalmology from 1949 to 1961. In 1955, he moved ophthalmology to the Mayo Building, where it is still housed (Fig. 9). Rucker published 98 journal articles, chapters, and books. In his first annual review of neuro-ophthalmology for the Archives of Ophthalmology in 1950, he stated that “the literature in this field is composed largely of unrelated and unexplained bits, mostly in the form of case reports” and “much of the literature on neuro-ophthalmology concerns rare diseases of little clinical significance” (6). In 1952 he decided that “during the past year, the number of published papers dealing with some phase of neuro-ophthalmology increased over that of preceding years. This is evidence neither of newly aroused interest in the field nor of any remarkable progress; it is merely that more people are writing papers” (7).
Rucker retired in 1967 and received the Howe Medal from the AOS in 1971 (Fig. 10).

Robert W. Hollenhorst completed medical school at the University of Minnesota, obtaining a BS in 1937, an MB in 1940, and an MD in 1941. A 3-month internship and 1 year of hospital service preceded his service in the army. He completed his ophthalmology residency at the Mayo Clinic in 1948. During that time, he reports that “I didn’t get a speck of neuro-ophthalmology experience.”

Hollenhorst joined the Mayo staff as a general ophthalmologist in 1949, and after 8 years in practice, decided that he did not enjoy surgery because there were “too many weekend and night worries.” He had become adept at ophthalmoscopy, so he fastened onto vascular disease and the eye, developing an interest in the ophthalmodynamometer, which had been popularized by Wagener. Hollenhorst had seen cholesterol emboli in many patients with stroke for approximately 10 years before publishing his observations (8,9). (It was J. Lawton Smith, MD, who later coined the term “Hollenhorst plaque.”) Hollenhorst went on to prove in the laboratory that cholesterol crystals released into the carotid circulation would lodge within the retinal vessels in monkeys, dogs, cats, and rabbits (10). He considers these studies his most significant contribution to neuro-ophthalmology.

Along with Henderson, Hollenhorst reported the first uses of intramuscular and topical cortisone in eye diseases (11,12). After publishing 11 chapters and 85 journal articles, he retired in 1979. He was awarded the Howe Medal of the AOS in 1986 (Fig. 11).

Originally from Kentucky, Thomas P. Kearns, MD, went to the University of Louisville for undergraduate studies (AB, 1943) and medical school (MD, 1946). He had learned about retinoscopy from an uncle and performed plane mirror and streak retinoscopic refractions in the army. After a locum tenens spent delivering babies, he was convinced that ophthalmology was the field to pursue. After his ophthalmology residency at Mayo, Kearns joined the staff in 1949 in the medical/neuro-ophthalmology, perimetry, and hospital consultation sections.

Rucker prompted Kearns (Fig. 12) to learn pathology, the basis for his later work on flat retinal preparations and the demonstration of fat emboli in the retina (13). He collaborated with Dale C. Smith, MD, an ophthalmology fellow, to produce Terson syndrome in monkeys and optic nerve sheath hemorrhage without direct connection to a subarachnoid hemorrhage (14). Working with William B. Glew, MD, a Mayo ophthalmology resident and later chair

FIG. 10. C. Wilber Rucker, MD, in 1961, seated at the control panel of the electronic pupillograph. Mary Cronin, an ophthalmic technician, is the subject, and Kenneth N. Ogle, PhD, is looking on. (Reproduced with permission from Henderson JW. Ophthalmology at Mayo, Historical Perspectives 1883–1972, private publication, 1981.)

FIG. 11. Robert W. Hollenhorst, MD, in 1982, wearing the presidential medal of the American Ophthalmological Society. (Reproduced with permission from the Transactions of the American Ophthalmological Society, 1982;LXXX:xii.)
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FIG. 12. Thomas P. Kearns, MD, in 1990. (Reproduced with permission from the American Academy of Ophthalmology.)

of ophthalmology at the Washington Hospital Center, and Hiram E. Essex, PhD, chair of the physiology department, Kearns tried to duplicate work performed at the beginning of the twentieth century in Germany, in which intracranial hypertension was produced in dogs with intracranial sponges. Unable to duplicate this work in dogs, they developed a better model using intracranial balloons to produce intracranial hypertension in monkeys (15). In 1958 they published the first photograph of experimental papilledema (16). This publication stimulated later work by Sohan S. Hayreh, MD, and Thomas R. Hedges, Jr, MD.

Kearns considers his greatest personal achievement the description of the syndrome that now bears his name, the Kearns-Sayre syndrome, reported in 1958 in conjunction with Mayo neuropathologist George P. Sayre, MD (17). Their original patients presented with syncopal spells that had been assumed to be psychogenic. Kearns noted peculiar retinal pigment epithelial changes and chorioretinopathy. He submitted his paper on the Kearns-Sayre syndrome as his AOS thesis with seven additional cases. It was turned down for lack of electrophysiologic and pupillographic testing. After learning about electro-oculography, electroretinography, and dark adaptation studies, the results of which were added to his manuscript. This version was published by the AOS (18).

Kearns coined the term “bull’s-eye maculopathy” as a description for chloroquine retinopathy in an article published in 1966 and co-authored with Hollenhorst (19). Presenting a case at a meeting at the Wilmer Ophthalmological Institute of Johns Hopkins University, Kearns declared the findings to be pathognomonic for chloroquine retinopathy. But A. Edward Maumenee, MD, then chair of ophthalmology, pulled out a slide showing a very similar finding in a patient with macular degeneration. Kearns was forced to concede that the “bull’s eye” was not entirely pathognomonic for chloroquine retinopathy.

Hollenhorst and Kearns noticed that several non-diabetic patients manifested a unilateral retinopathy similar to that seen in diabetic patients. Rucker suggested that diabetes would develop in these patients later in life. But Kearns argued that these findings were secondary to hypoxia of the retina from carotid artery stenosis. At an AOS meeting, he defended his view that these findings were not a manifestation of a retinal vein occlusion (20). Rucker had called this finding “venous stasis retinopathy,” a term that Kearns accepted, although he says that he would have preferred to call it “chronic ischemic retinopathy.”

Kearns recalls that one day, as he was trying to determine whether to prescribe single reading glasses or bifocals, he asked his patient what kind of work he did. The answer came back as “Wahl, I'm the senior Senatuh [sic] from Texas.” The speaker was, of course, Lyndon B. Johnson.

In addition to his 86 publications, Kearns taught at the Lancaster Course in Maine for 15 years and was the first to use the Perkins tonometer at Mayo. He served as a member of the American Board of Ophthalmology and the Residency Review Committee for Ophthalmology and as president of the American Academy of Ophthalmology in 1986. He retired from the Mayo Clinic in 1987, receiving the Howe Medal from the AOS in 1994.

James C. Trautmann, MD, started his residency in ophthalmology at the Mayo Clinic in 1964. Before his residency, he had attended the University of Minnesota for his BA (1950) and MD (1954). After finishing his residency, he joined the Mayo staff in the section of medical and neuro-ophthalmology.

Trautmann wrote his master's thesis on the velocity of the pursuit phase of optokinetic nystagmus in 13 healthy subjects in 1966. His 41 publications concentrated on neuro-ophthalmology with an emphasis on ocular manifestations of diabetes, reflected in eight journal articles. He retired from Mayo in 1991 (Fig. 13).

The Mayo tradition in neuro-ophthalmology continues to be strong under the auspices of Brian R.
ACKNOWLEDGMENTS

This work was profoundly influenced by the personal interviews with John W. Henderson, MD, William B. Glew, MD, Thomas P. Kearns, MD, and Robert W. Hollenhorst, MD. A special thanks to Kristi Hunter for her assistance with archived photographs and to Renee Ziemer for historic data from the Mayo Historical Unit. Thanks also to Jay C. Eric, MD, for his help and expertise with the manuscript.

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Intracranial Hypertension Associated With Transverse Myelitis

To the Editor:

Raised intracranial pressure has been reported rarely in demyelinating central nervous system disease. We recently encountered a case of transverse myelitis with simultaneous intracranial hypertension. This association of monophasic spinal cord demyelination and concurrently raised intracranial pressure has not, to our knowledge, been reported previously.

A 25-year-old woman presented with a 12-week history of paresthesias in both hands, upper trunk dysesthesias, Lhermitte phenomenon, postural headaches, and visual obscurations. She had no pertinent history and did not use any drugs.

Examination showed a suspended sensory level between C3 and T12. Tone and power were normal. Reflexes were brisk but equal in the four limbs and plantar responses were flexor. Cranial nerve, cerebellar, and sphincter functions were unimpaired. Visual acuity was normal but Humphrey visual fields showed enlarged blind spots. Fundoscopy revealed bilateral papilledema with several hemorrhages. Her weight was 94 kg with a body mass index of 36.

Magnetic resonance imaging and venography of the brain were normal. Magnetic resonance imaging of the cervical cord showed a longitudinal hyperintensity on sagittal T2-weighted images from C3 to C4, suggestive of a demyelinating plaque (Fig. 1). The lumbar puncture opening pressure was 440 mm of water and cerebrospinal fluid examination showed 45 lymphocytes/μL, a protein of 70 mg/dL, and a glucose of 2.5 mmol/L (serum glucose of 4.0 mmol/L). Oligoclonal bands were present. Blood count, inflammatory markers, electrolytes, renal and liver functions, thyroid function, angiotensin-converting enzyme were normal. Serologies for syphilis, herpes, Epstein-Barr, cytomegalovirus, and Borrelia burgdorferi were negative, as were antinuclear antibodies. Chest x-ray was normal.

No corticosteroid treatment was administered and the patient made a complete recovery from the myelitis within 6 months. She was treated with acetazolamide 500 mg/d and her headaches, visual symptoms, and optic disc edema disappeared within 3 months. In a follow-up of over 3 years, no new clinical findings have appeared.

Central nervous system demyelination with raised intracranial pressure has been described very rarely (1–4). Some authors (1–3) have speculated that raised intracranial pressure is related to mechanical obstruction of cerebrospinal fluid flow by plaques. In an article published in Russian, Skoromets et al in 1991 (4) suggested that intrathecal immunoglobulin synthesis results in osmotic and oncotic cerebrospinal fluid pressure changes, thereby disturbing the blood–brain barrier and elevating intracranial pressure. Contrasting with the scarcity of English language reports, this article surprisingly reported raised intracranial pressure (220–380 mm of water) in 40 patients during an exacerbation of multiple sclerosis. All patients were said to be symptomatic from the raised pressure, with headaches, nausea, vomiting, and confusion. The appearance of the optic discs was not described.

In a later report, Newman et al (5) proposed that the association of intracranial hypertension with auto-immune conditions such as systemic lupus erythematosus (6) suggests immune complex deposition within the arachnoid villi as a potential mechanism.

FIG. 1. Sagittal T2-weighted magnetic resonance imaging shows longitudinal hyperintensity at C3-C4 indicative of demyelination.
A coincidental association is possible, of course, because our patient was a young and obese woman. Our case is distinctive in that she did not, unlike the three patients of Newman et al (5), have clinically-definite multiple sclerosis, but instead had a monophasic illness with imaging abnormalities limited to the spinal cord and no other manifestations 5 years after onset. Such an association has not, to our knowledge, previously been described.

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REFERENCES

Persistent Visual Loss from Neurotrophic Corneal Ulceration After Dorsolateral Medullary Infarction (Wallenberg Syndrome)

To the Editor:

Neurotrophic keratopathy is a complication of fifth cranial nerve or ganglion dysfunction (1). Decreased corneal sensitivity can also occur from interruption of the spinal fifth nerve complex (2). However, few reports have described ulcerative keratitis complicating loss of corneal sensation associated with lesions of the medulla such as syringomyelia or infarction (3,4). We recently encountered a patient in whom this complication developed after a dorsolateral medullary infarction (Wallenberg syndrome).

A 48-year-old hypertensive, hyperlipidemic man had the abrupt onset of vertigo, imbalance, right facial numbness, and weakness of his left arm and leg. The next day, diffusion-weighted and fluid-attenuated inversion recovery magnetic resonance (MR) imaging (Fig. 1) revealed infarction of the right dorsolateral medulla. MR angiography showed normal carotid and vertebral arteries. After physical rehabilitation, he was able to walk with a cane, but he had persistently reduced pain and temperature sensation of the right side of his face that was not in an onion-skin pattern. He had no lagophthalmos or facial motor dysfunction.

Two months after the acute stroke, he had painless inflammation OD with a corneal epithelial defect, stromal edema and infiltration, and a hypopyon (Fig. 2). He had no sensation of the right cornea to a cotton wisp but could detect the gentlest setting of the Cochet-Bonnet esthesiometer applied to the left cornea. Corneal scrapings yielded Proteus mirabilis, Enterobacter cloacae, and Staphylococcus epidermidis. After topical therapy with ceftazidime and tobramycin, a continuous-wear soft contact lens was fitted with frequent use of preservative-free lubricants. Because of a persistent corneal epithelial defect, a lateral tarsorrhaphy was later performed. His ocular surface gradually healed, but vision remained counting fingers because of a residual corneal opacity.

We are unaware of previous reports of this complication after medullary infarction. Preventive strategies may be needed to avert vision-limiting complications and
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FIG. 1. Axial fluid-attenuated inversion recovery magnetic resonance imaging showing region of hyperintensity in the right dorsolateral medulla.
FIG. 2. Epithelial defect of the lower two-thirds of the right cornea associated with loss of corneal sensation. Superinfection of neurotrophic keratopathy in patients who lose corneal sensation in this circumstance.

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REFERENCES

Isolated Granulomatous Uveitis Presenting Twenty-Two Years before Multiple Sclerosis

To the Editor:
An association exists between granulomatous uveitis and multiple sclerosis (MS) (1–4). Rarely does the uveitis antedate the other manifestations of MS. We examined a patient who had presented with chronic isolated granulomatous anterior uveitis 22 years before she demonstrated the first clinical manifestations of MS, which was confirmed at autopsy 4 years later.

Bilateral, granulomatous anterior uveitis and anterior vitreous inflammation developed in a 36-year-old woman in 1975. Angiotensin-converting enzyme, lysozyme, purified protein derivative, syphilis serologies, and chest roentgenogram were normal. Gallium scan demonstrated increased uptake in the mediastinum, lacrimal, and parotid glands. Sarcoidosis was presumptively diagnosed. Her uveitis became chronic with intermittent exacerbation of inflammation.

In 1997, a spastic right hemiparesis, bladder dysfunction, and gait disturbance developed. Her symptoms remitted over the next 2 months. In 2001 she awoke with binocular, horizontal diplopia. She denied headache, blurred vision, dysarthria, or vertigo. Visual acuities were 20/100 OD and 20/60 OS. Pupils were irregular and poorly reactive. Neither eye adducted fully. She had a slow spastic gait, a mild right hemiparesis, pathologically brisk reflexes, and a right extensor plantar response.

Cerebrospinal fluid revealed a mild lymphocytic pleocytosis and a markedly elevated cerebrospinal fluid immunoglobulin G index, immunoglobulin G-to-albumin ratio, and immunoglobulin G synthesis rate. Brain magnetic resonance imaging showed multiple ovoid periventricular, subcortical, and infratentorial white matter hyperintensities on T2 and fluid-attenuated inversion recovery sequences (Fig. 1). Midbrain lesions involved the periaqueductal region and both medial longitudinal fasciculi. Several lesions demonstrated enhancement.

Nine months later, she died of urosepsis. At autopsy, multiple microscopic foci of chronic demyelination were present throughout the neuroaxis (Fig. 1).

Uveitis in MS patients usually appears as an intermediate uveitis sometimes associated with retinal periphlebitis (1–4). Several reports, however, describe patients with clinical MS and granulomatous anterior uveitis, characterized by large, mutton fat keratic precipitates. Bioussue et al (2) reported uveitis in 11 patients occurring up to 2 years before the onset of neurologic symptoms of MS. Among six MS patients with chronic granulomatous anterior uveitis reported by Acar et al (3), the uveitis preceded neurologic symptoms in two patients by 4 and 13 years. However, unlike our case, there was no pathologic confirmation of MS in any of these previously reported patients with uveitis.

Therefore, it is conceivable that these patients had neurosarcoidosis rather than MS. The neuroimaging, clinical course, and spinal fluid analysis of neurosarcoidosis and MS can be indistinguishable. Each disease can demonstrate
FIG. 1. Magnetic resonance fluid-attenuated inversion recovery imaging shows areas of signal hyperintensity in cerebral periventricular white matter (A) and periaqueductal region in midbrain (C) that correspond to demyelinated plaques (arrows) by histologic autopsy examination (B, D, Luxol fast blue, hematoxylin and eosin). Many of the lesions in the subventricular white matter are partially myelinated shadow plaques (B, single arrows), suggestive of remyelination. Images B and D were obtained by scanning stained glass slides at 4000-pixel per inch resolution using an ArtixScan 4000tf scanner (Microtek, Redondo Beach, CA), followed by conversion to grayscale and contrast adjustment using Photoshop (Adobe Systems, San Jose, CA).

There is one report of a patient with autopsy-proven MS and histopathologic evidence of granulomatous uveitis (4). However, the authors do not discuss the temporal relationship of the clinical onset of uveitis and neurologic symptoms.

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ovoid periventricular T2 and fluid-attenuated inversion recovery signal hyperintensities that may enhance. The cerebrospinal fluid analysis in both conditions may reveal intrathecal immunoglobulin synthesis and oligoclonal bands (5,6).
**Adler's Physiology of the Eye: Clinical Application, Tenth Edition**


**Scope:** This tenth edition of Adler's Physiology of the Eye is a comprehensive, single-volume, multi-authored textbook of ocular physiology designed to be a reference text for preclinical scientists and clinicians. It emphasizes clinical applications of the exponentially expanding knowledge base of ocular physiology, morphology, and molecular biology.

**Contents:** The book is divided into 14 sections, each with a separate editor. Each section covers broad topics, including the ocular surface, the cornea and sclera, the lens, optics and refraction, accommodation and presbyopia, aqueous humor hydrodynamics, the vitreous, the retina, visual perception, the optic nerve, the central visual pathways, the pupil, ocular circulation, and extraocular muscles/eye movements. Topics covered include anatomy, development, physiology, and pathophysiology. Each chapter is a thoroughly referenced (more than 500 references in some chapters) up-to-date review with extensive figures, illustrations, diagrams, and clinical photographs.

Of particular interest to neuro-ophthalmologists are the sections about retina, optic nerve, visual perception, the central visual pathways, the pupil, extraocular muscles, and eye movements. The visual perception section provides a comprehensive overview of several areas rarely discussed, including entoptic phenomena, visual acuity, early visual processing of spatial form, binocular vision, temporal properties of vision, development of vision in infancy, perimetry and visual field testing, color vision, and visual adaptation. The central visual pathways section is organized anatomically, including chapters on the retina-geniculate projections, the lateral geniculate nucleus, the primary visual cortex, and the extrastriate cortex, as well as a chapter on visual deprivation. The final section on extraocular muscles and eye movements has three chapters, with the latter two including explanations of three-dimensional rotations of the eye and the neural control of eye movements. Interesting new additions to the text include updated descriptions of the neural circuitry of the retina, ophthalmic facial anatomy, and ocular circulation.

**Strengths:** This is an updated and revised edition of a classic. It is arguably the most important single-volume reference for scientists and clinicians seeking information or insight into any aspect of vision science. At the same time, it is enjoyable to read, chapter by chapter, for anyone who is fascinated by the workings of the eye and its brain connections. The chosen authors are all recognized experts in their fields, and the text covers all aspects of the visual system. Information gathered from basic science research is used to explain ocular physiology. Clinical correlations aid in the understanding and application of the basics of vision science to patient care. The figures and tables are clear and complement the text well. The chapters on the pupil, the optic nerve, ocular circulation, the extraocular muscles, three-dimensional rotations of the eye, and the neural control of eye movements are spectacular.

**Weaknesses:** A minor criticism is that many of the photographs of the eye and histologic sections would be better viewed as color reproductions. There is a small color plate section in the back of the book that includes 22 color figures that seem to be arbitrarily chosen. Like any other multi-authored text, there is some unevenness to the writing style.

**Recommended audience:** This book is intended for preclinical scientists and clinicians but is equally useful for ophthalmologists and students of vision science.

**Critical appraisal:** The editors have created a comprehensive, up-to-date text on ocular physiology. This book should be an invaluable addition to any neuro-ophthalmologist's collection. Dr. Adler would be proud of this latest version of his classic text.

**Nicholas J. Volpe, MD**

Scheie Eye Institute
University of Pennsylvania
Philadelphia, Pennsylvania

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**Ophthalmology, Second Edition**


**Scope:** This is a multi-authored textbook divided into 12 parts, with section editors overseeing each part. The far right sides of the pages in each section are tagged with a color for quick reference to that section. The sections are: 1) genetics and ocular embryology; 2) optics and refraction; 3) refractive surgery; 4) lens; 5) cornea and external disease; 6) strabismus; 7) orbit and ocularplastics; 8) retina and vitreous; 9) intraocular tumors; 10) uveitis and other intraocular inflammations; 11) neuro-ophthalmology; and 12) glaucoma.

The book covers essentially all of ophthalmology. It has many excellent tables, diagrams, and color photographs.

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Susan M. Ksiazek, MD
The University of Chicago
Chicago, Illinois

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**Diagnostic and Interventional Neuro-Radiology: A Multimodality Approach**

**Scope:** This is a multi-authored, highly illustrated text that attempts to briefly encompass all of neuroradiology in short focused segments. It is not intended for in-depth study by neuroradiologists or even residents specializing in neuroradiology, but is a reasonable overview for non-neuroradiologists, and for radiologists attempting to keep abreast of new developments.

The book is divided into two major sections titled “Diagnosis: Imaging Procedures” and “Treatment: Interventional Procedures.” The former is further subdivided into cranio-cerebral diseases, including sections on diagnostic methodology, malformations, traumatic lesions, tumors and tumor-like diseases, vascular diseases, infection and inflammation, demyelinating and degenerative diseases, intracranial lesions, and effects of medical conditions. A second section within “Diagnosis: Imaging Procedures” is devoted to spinal diseases. This includes subsections on normal findings, malformations, developmental abnormalities, traumatic lesions, spinal tumors and tumor-like diseases, vascular diseases, infections and inflammations, demyelinating and degenerative diseases, and other diseases of the spinal column. A third section within “Diagnosis” includes neuromuscular diseases. This includes sections on progressive muscular dystrophy, neurogenic diseases, myositis, and other muscular diseases.

The second half of the text discusses interventional procedures and treatment, including subsections on endovascular treatment of cranio-cerebral diseases. There are chapters on materials and methods, treatment of arteriovenous malformations, arteriovenous fistulas, cerebral aneurysms, and pre-operative devascularization of hypervascular tumors. There are also presentations on thrombolysis and angioplasty, although these tend to be superficial. The section on spinal disease includes treatment of angioplasties and fistulas, preoperative devascularization of tumors, percutaneous nucleotomy, and pain management.

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**Disorders of Myelin in the Central and Peripheral Nervous Systems**

**Scope:** This is a multi-authored compilation of current clinical and basic science information pertaining to disorders of myelin in both the central and peripheral nervous systems.
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Weaknesses: There is an occasional chapter that does not flow with the rest of the section. Some sections rely heavily on a single author, others on many authors with uneven results. The textbook is heavy and awkward to carry.

Recommended audience: Ophthalmology residents and general ophthalmologists should find this an excellent resource.

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systems. Each of the 18 chapters contributes to a cohesive and concise review of the genetics, immune mechanisms, pathology, and clinical differentiation of disease processes directly affecting myelin, including multiple sclerosis, hereditary leukodystrophies, human T-cell lymphotrophic virus type I-associated myelopathy/tropical spastic paraparesis, HIV-related dysmyelination, progressive multifocal leukoencephalopathy, Guillain-Barré syndrome, and more.

Many of the authors are well-known researchers and clinicians who share personal and thoughtful insight into directions for future research areas. Up-to-date, extensive references are included at the end of each chapter, and a 15-page atlas of color plates enhances understanding of the textual concepts.

Strengths: For its 363 pages, this book manages to include a remarkable amount of material ranging from reviews of causative factors in multiple sclerosis to electrophysiologic diagnostic criteria for Guillain-Barré syndrome to principles of magnetic resonance imaging and DNA microarray analysis. The text is heavily focused on discussion of all aspects of multiple sclerosis, including a well-organized and interesting chapter called “Experimental Autoimmune Encephalomyelitis and Multiple Sclerosis: From Bench to Bedside.” In this chapter, the roles of various immunologic contributors to the demyelinating process are considered in the context of experimental research and current and future therapeutic applications. Concise chapters entitled “Magnetic Resonance Imaging in Disease Progression in Multiple Sclerosis” and “Management of Multiple Sclerosis: Disease-Modifying Treatments” summarize the current approach to utilization of these entities based on recent trials.

Weaknesses: Differences in writing style inherent in a multi-authored book are present in this text, with some chapters of higher quality than others. Organization of the text in certain segments of the book is somewhat unusual. For example, in the midst of several chapters on multiple sclerosis, there is a chapter that elaborates on interpretation of electrophysiologic criteria of peripheral neuropathies, requiring a major shift in mind set from central to peripheral demyelination and back again if one were reading the chapters consecutively.

Recommended audience: This book is most appropriate for anyone involved in the care of demyelinating disorders.

Critical appraisal: Overall, this book is a highly inclusive yet compact review of central and peripheral demyelinating disease with insight into the research and perspectives of its respected authors. It is unique in focusing on central or peripheral demyelination processes.

Janet C. Rucker, MD
Case Western Reserve University School of Medicine
Cleveland, Ohio

Perceptual Learning


Scope: This is a multi-authored book consisting of chapters written by scientists in perceptual learning. It intends to be a comprehensive presentation of advances made in the past decade in the understanding of perceptual learning. The editors define perceptual learning as “any relatively permanent and consistent change in the perception of a stimulus array following practice or experience...[that is] relatively independent from conscious experience...[and that] seems to directly modify the neuronal pathways active during processing of the task...” Thus, a purely sensory experience that modifies neuronal pathways and leads to an alteration in perception and implicit memory.

The information presented deals with changes in primary sensory cortices as a result of perceptual learning in the adult. Modern studies of perceptual learning have expanded the concept of cortical plasticity from what was thought to be an early-in-life phenomenon to a process that continues after birth. The “classical view” dictates that such change should not be found past the early postnatal period. However, the crucial finding represented by this collection of articles is that synaptic plasticity continues to be a factor that subtly reshapes even primary sensory cortices throughout adulthood.

The book is divided into four sections. The first section (seven chapters), “Anatomy and Physiology,” deals with changes at the neuronal and synaptic level with emphasis on interneuronal connections. The second section (five chapters), “Low-Level Psychophysics,” covers topics such as cognition and learning of visual objects and tasks. The fourth section (three chapters), “Modeling,” presents models that attempt to tie all of this material together. One chapter is particularly interesting because it reviews experimental data regarding the changes found in the receptive fields of cells in the primary visual cortex after retinal lesions, cortical lesions, or artificially induced scotomas.

Strengths: The chapters are a balanced mix of relatively broad reviews and are clearly written, detailed presentations of specific experiments and topics. Especially informative are broadly oriented chapters by Manfred Fahlle, “Introduction”; Siegrid Lowel and Wolf Singer, “Experience-Dependent Plasticity of Intracortical Connections”; Hubert Dinse and Michael Merzenich, “Adaptation of Inputs in the Somatosensory System”; Annette Sterr, Thomas Elbert, and Brigitte Rockstroh, “Functional Reorganization of Human Cerebral Cortex and Its Perceptual...
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The chapters are profusely referenced, which allows this to be a good, solitary, up-to-date source for further study.

**Weaknesses:** This is not a textbook and thus is not a start-to-finish development of the topic. It is a specialized collection that assumes a good knowledge of cortical organization and functioning. Some of the more experiment-oriented chapters will be of interest to only a narrow spectrum of readers. Fadde suggests in the Introduction that perceptual learning offers hope for disorders such as anisometropia, prosopagnosia, visual field defects, and Alzheimer disease, but he does not present any supportive evidence for this claim. Throughout the text there are also occasional references to visual training techniques that might reduce visual deficits on the basis of perceptual learning without a critical review of the subject or other plausible explanations for recovery.

**Recommended audience:** Because of the extensive review of experimental data, the text is directed toward scientists in the field of brain physiology and plasticity. However, clinicians in specialties associated with neuroscience may find this book interesting.

**Critical appraisal:** The selection of topics and authors demonstrates that this collection was well thought out as a vehicle to introduce current thinking on the topic. The presentations are readable and attention was clearly paid to reducing jargon. Evidence is given in enough detail to allow the reader to understand the basis of the conclusions and speculations.

**Mark W. Dubin, PhD**
Department of Molecular, Cellular, and Developmental Biology
University of Colorado
Boulder, Colorado

**Victoria S. Pelak, MD**
Departments of Neurology and Ophthalmology
University of Colorado School of Medicine
Denver, Colorado

**Binocular Anomalies: Diagnosis and Vision Therapy, Fourth Edition**

**Scope:** This book is the most complete text available detailing current optometric concepts of the physiology of normal binocular vision, pathologic binocular states, and various types of vision therapy used to correct them. It also chronicles the history of optometric vision training in the United States and Europe.

The text is subdivided into three sections: Diagnosis, Treatment, and Techniques. Following the text are numerous appendices, a lengthy self-assessment examination, and a glossary and index.

The Diagnosis section commences with a section on normal binocular vision and proceeds to discuss ways to examine eye movements, ocular alignment, and degree of binocular cooperation. Further chapters cover diagnosis and prognosis of comitant strabismus and strabismus caused by neurologic and orbital disease. The section concludes with a brief discussion of nystagmus.

The Treatment section nicely reviews the current optometric concepts of treatment of amblyopia, abnormal retinal correspondence, strabismus, and nystagmus. A final chapter examines problems with "vision efficiency" and includes common causes of asthenopia and vague visual symptoms such as those attributed to aniseikonia, accommodation abnormalities, vergence abnormalities, and problems with pursuit and saccadic eye movements.

The final section is an exhaustive collection of techniques for visual training in the office and at home. It includes much information with which the ophthalmologist will be quite familiar (occlusion, vergence exercises, orthoptic and synoptophore training), but the bulk of matter discussed will likely be foreign to most medical readers (Remy separator, chiasitic fusion, useful field of view). The final chapter discusses different practice scenarios in which an optometrist may use vision training and lists vision therapy techniques for all conditions covered in the book.

In the appendices is a joint statement from the American Academy of Optometry and the American Optometric Association on vision, learning, and dyslexia, which is primarily at odds with the parallel statement on vision training for reading problems from the American Academy of Ophthalmology and the American Association of Pediatric Ophthalmology and Strabismus.

**Strengths:** There is much in this book for which the ophthalmologist and optometrist will find common ground. The sections on accommodation, stereopsis, strabismus evaluation, vision testing in children, and sensory adaptations to strabismus are well-written and concise. Amblyopia management is well-covered and even includes optical penalization and levodopa treatment. The sections on techniques of vision training (which ophthalmologists may not agree with) read very well and are extremely thorough. The authors are frank with their biases and state that in most cases of significant heterophoria and intermittent strabismus" vision training should be recommended.

**Weaknesses:** The neurology of eye movements is covered sparsely, with little attention to current neuroanatomic and...
Concomitants”; and Pawan Sinha and Tomaso Poggio, “High-Level Learning of Early Visual Tasks.”

The chapters are profusely referenced, which allows this to be a good, solitary, up-to-date source for further study.

Weaknesses: This is not a textbook and thus is not a start-to-finish development of the topic. It is a specialized collection that assumes a good knowledge of cortical organization and functioning. Some of the more experiment-oriented chapters will be of interest to only a narrow spectrum of readers. Fahl suggests in the introduction that perceptual learning offers hope for disorders such as amblyopia, prosopagnosia, visual field defects, and Alzheimer disease, but he does not present any supportive evidence for this claim. Throughout the text there are also occasional references to visual training techniques that might reduce visual deficits on the basis of perceptual learning without a critical review of the subject or other plausible explanations for recovery.

Recommended audience: Because of the extensive review of experimental data, the text is directed toward scientists in the field of brain physiology and plasticity. However, clinicians in specialties associated with neuroscience may find this book interesting.

Critical appraisal: The selection of topics and authors demonstrates that this collection was well thought out as a vehicle to introduce current thinking on the topic. The presentations are readable and attention was clearly paid to reducing jargon. Evidence is given in enough detail to allow the reader to understand the basis of the conclusions and speculations.

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Weaknesses: The neurology of eye movements is covered sparsely, with little attention to current neuroanatomic and
physiologic concepts. As would be expected, the comments on strabismus surgery are extremely shallow and incomplete. None of the results of any of the NEI-sponsored amblyopia treatment trials is included, a striking deficiency because optometrists participated in these trials. The authors frequently refer to use of the Visagraph to record eye movements, even though there are no normative data for this instrument and it has not been appropriately studied. Divisions of accommodative esotropia into refractive and nonrefractive types are not mentioned, nor are results of any of the infantile esotropia observational studies sponsored by NEI. The concepts on Duane retraction syndrome are outdated and there is no mention of the possibility of heterotopic muscle pulley systems as a cause of strabismus. Current understanding of dyslexia resulting from phonemic translation problems rather than vision abnormalities is singularly absent.

Finally, some of the therapies recommended will be regarded as heresy by many ophthalmologists, including saccadic efficiency training to improve reading, physical therapy of the extraocular muscles for cranial nerve palsy, hypnotherapy for intractable diplopia, and vision training exercises for congenital nystagmus. The authors conclude that the AAO/AAPOS policy statement on vision and reading reflects a “lack of understanding” on the part of these organizations of the pathophysiology and treatment of these conditions. What the authors have not pointed out, however, is that the literature contains absolutely no well-designed, sufficiently powered, randomized, controlled clinical trials to support the efficacy of vision training for any of the conditions for which it is recommended.

**Recommended audience:** The text is dedicated to “students and practitioners of binocular vision.” Certainly it is of importance to those in the optometric community who use vision training in their practices. Ophthalmologists and neurologists may find certain sections a good source of information.

**Critical appraisal:** This is a very readable book by highly experienced practitioners of vision therapy. Ophthalmologists and neurologists interested in strabismus, eye movement disorders, and binocular function should at least peruse this book. Although readers will likely find many areas of disagreement and lack of scientific evidence for therapies promoted in the text, it will at least facilitate critical arguments and perhaps promote an open and frank dialogue with the optometric community on designing quality scientific studies.

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Oklahoma City, Oklahoma
Jonathan D. Wirtschafter, MD  
(1935–2004)

On August 9, 2004, our colleague Jonathan D. Wirtschafter died at age 69 of amyotrophic lateral sclerosis. A memorial service was held on August 11, 2004 at Temple Israel in Minneapolis, with Rabbi Marcia Zimmerman officiating. The internment took place at Adath Yeshurun Cemetery in Minneapolis.

At the memorial service, Jonathan was remembered as a loving parent and spouse, friend, and teacher. He was a loving and caring husband to his wife Carol and a loving father to his five children, Joshua, Jacob, Benjamin, David, and Brooke. He was also the proud grandparent of 10 grandchildren.

Jonathan was born in 1935 and grew up in Cleveland. He graduated from Reed College in Portland, Oregon in 1956 and from Harvard Medical School in 1960. He served as a neurology resident at Good Samaritan Hospital in Portland from 1961 to 1963 and as an ophthalmology resident at the Wilmer Eye Institute of Johns Hopkins University from 1963 to 1966. The next year, he was a neurology fellow at the New York Neurological Institute of Columbia-Presbyterian Medical Center.

His first academic post was as the University of Kentucky in 1967, where he started an ophthalmology residency training program, rose to the rank of full professor in 1972, and served as the first chairman of the ophthalmology department from 1974 to 1977. During a 1-year sabbatical leave in Israel in 1973, he drove a Volkswagen bus across Europe with his wife and their five children, the youngest being 18 months old. When the Yom Kippur War broke out that year, he interrupted his sabbatical to work the night shift at a Jerusalem hospital.

He was appointed to the ophthalmology faculty at the University of Minnesota Medical School in 1977 and served as director of the neuro-ophthalmology service until his retirement from full-time clinical practice in 2001. He held joint appointments in the neurology and neurosurgery departments. Ophthalmology residents at the University of Minnesota chose him as Teacher of the Year on four occasions.

In the neuro-ophthalmic community, he was known for his interests in treatment of blepharospasm and hemifacial spasm. He pioneered the use of doxorubicin, currently in clinical trials. As director of the neuro-ophthalmology/orbit/oculoplastics fellowship at Minnesota, he trained 13 fellows between 1981 and 2001. He served on the editorial board of Survey of Ophthalmology, Journal of Neuro-Ophthalmology, and Perspectives in Ophthalmology. The holder of several patents and the recipient of many research grants, some of which supported his pioneering work on doxorubicin chemomymectomy, he was an author or co-author of 148 journal articles. He also co-authored several textbooks published by the American Academy of Ophthalmology, including Ophthalmic Anatomy (1981), Computed Tomography: An Atlas for Ophthalmologists (1982), and Magnetic Resonance Imaging and Computed Tomography: Clinical Neuro-Ocular Anatomy (1992). He was an active member of the Benign Essential Blepharospasm Foundation, which provides research grants, education, and psychosocial support to patients with facial spasm disorders. He was an active member of NANOS, serving as president from 1996 to 1998. In 2004, he received the NANOS Distinguished Service Award.

After retiring from active clinical practice in 2001, he continued to participate in teaching, laboratory research, clinical trials, and scientific writing. Even as his illness began to limit his mobility, he persevered in research. His most recent work, performed in conjunction with Linda
McLoon, PhD, and Deborah Ferrington, PhD, demonstrated continuous myofiber remodeling in adult extraocular muscles (1).

In 2003, fellow faculty members in the ophthalmology department at the University of Minnesota, as well as colleagues and friends, honored his many contributions to teaching, research, and patient care with the establishment of the Jonathan D. Wirtschafter Visiting Lectureship. Donations to the lectureship may be sent to the Vision Foundation, University of Minnesota Ophthalmology Department, Box 493, 420 Delaware Street SE, Minneapolis, MN 55455.

Howard D. Pomeranz, MD, PhD
Minneapolis, Minnesota

REFERENCE

Upcoming Meetings

February 2 to February 4, 2005
International Stroke Conference
New Orleans, Louisiana
http://strokeconference.americanheart.org/portal/strokeconference/se/
Contact: strokeconference@heart.org

February 12 to February 17, 2005
Copper Mountain, Colorado
Contact: (860) 586–7507

March 3 to March 6, 2005
American Society of Neuroimaging 28th Annual Meeting
Orlando, Florida
http://aswnet.org/meeting/meeting2005.shtml
Contact: asn@llmsi.com

March 9 to March 13, 2005
American Association of Pediatric Ophthalmology & Strabismus Annual Meeting
Orlando, Florida
http://www.aapos.org/annualmeeting05.htm
Contact: aapos@aao.org

March 18 to March 21, 2005
XXV Congress of the Pan American Association of Ophthalmology
Santiago, Chile
http://www.paaoo.org/congress.htm
Contact: info@paaoo.org

April 9 to April 16, 2005
57th Annual Meeting of the American Academy of Neurology (AAN)
Miami, Florida
http://am.aan.com/
Contact: membersservices@aan.com

April 16 to April 21, 2005
American Association of Neurological Surgeons Annual Meeting
New Orleans, Louisiana
http://www.aans.org/annual/
Contact: 847.378.6500, info@aans.org

May 1 to May 5, 2005
The Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting
Fort Lauderdale, Florida
http://www.arvo.org/AM/home.aspx
Contact: (240) 221–2900, arvo@arvo.org

May 21 to May 27, 2005
43rd Annual Meeting of the American Society of Neuroradiology (ASNR)
Toronto, Ontario, Canada
http://www.asnr.org/2005/
Contact: 650–574–0220, vgeisendorfer@asnr.org

May 25 to May 28, 2005
14th European Stroke Conference
Bologna, Italy
http://www.eurostroke.org
Contact: Hennerici@eurostroke.org

June 14 to June 18, 2005
Canadian Congress of Neurological Sciences Annual Meeting
Ottawa, Ontario, Canada
http://www.cns.org/cns≤_≤information/events.html
Contact: web@cns.org

June 18 to June 22, 2005
15th Meeting of the European Neurological Society
Vienna, Austria
http://www.ensinfo.com
Contact: info@akm.ch

June 23 to June 25, 2005
8th European Congress of Neuropathology
Amsterdam, The Netherlands
http://www.euro-cns.org/congresseur.php
Contact: a.vanschendel@amc.uva.nl
June 26 to 29, 2005
7th Meeting of the European Neuro-Ophthalmological Society (EUNOS)
Moscow, Russia
http://www.nsi.ru/events/eunos/
Contact: conf@nsi.ru

September 17 to September 20, 2005
9th Congress of the European Federation of Neurological Societies
Athens, Greece
http://www.efns.org/efns2005
Contact: elns05@kenes.com

September 25 to September 28, 2005
130th Annual Meeting of the American Neurological Association
San Diego, California
http://www.anetraoa.org/futurem=meetings.html
Contact: Julieratzloff@llmsi.com

September 25 to September 29, 2005
Joint Meeting of the 15th Congress of the European Society of Ophthalmology
103rd Annual Meeting of the German Society of Ophthalmology
Berlin, Germany
http://www.soe2005.org
Contact: soe2005@porstmann-kongresse.de

October 5 to October 8, 2005
European Association for Vision and Research (EVER)
Vilamoura, Portugal
http://www.ever.be
Contact: ever@skynet.be

October 8 to October 13, 2005
Congress of Neurological Surgeons 55th Annual Meeting
Boston, Massachusetts
http://www.neurosurgeon.org/meetings/meetingSites.asp
Contact: info@icns.org

October 15 to October 18, 2005
Annual Meeting of the American Academy of Ophthalmology (AAO)
Chicago, Illinois
http://www.aaao.org
Contact: meetings@aaao.org

November 5 to November 11, 2005
XVIII World Congress of Neurology
Sydney, Australia
http://www.wcn2005.com
Contact: info@wcn2005.com

November 12 to November 15, 2005
35th Annual Meeting of the Society for Neuroscience
Washington, DC
http://web.sfn.org/content/Meetings_Events/FutureandPastAnnualMeetings/index.html
Contact: info@sfn.org

February 20 to February 24, 2006
Joint Meeting of the XXX International Congress of Ophthalmology, the XVI Pan-American Congress of Ophthalmology, and the XVII Brazilian Congress of Prevention Blindness
Sao Paulo, Brazil
http://www.ophthalmology2006.com.br/
Contact: info@ophthalmology2006.com.br

November 29 to December 2, 2006
XVI International Neuro-Ophthalmology Society Meeting (INOS)
Tokyo, Japan
http://www.secretariat.ne.jp/inos2006/
Contact: inos@secretariat.ne.jp
The *Journal of Neuro-Ophthalmology* gratefully acknowledges the following 2004 reviewers:

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