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"Retinal Migraine" is an Oxymoron

Jacqueline M. S. Winterkorn, PhD, MD

Transient monocular visual loss remains a condition of uncertain and controversial pathophysiology. Its causes include inadequate blood flow, hypercoagulability, emboli or thrombi, and vasospasm. At various times in the medical history of the past hundred years, different hypotheses have been popular. After observing particulate matter passing through the retinal vascular bed in 1952, Fisher (1) suggested that most cases of transient monocular visual loss resulted from embolism. Recently, Trobe (2) reported that Fisher believes that the role of emboli has been overstated and that low perfusion of the retinal vascular bed is the predominant etiology. Nevertheless, the embolic theory has prevailed, and vasospasm has remained out of vogue for decades.

Although the signs of vasospasm—narrowing of the retinal vessels, boxcarring, and retinal blanching—have been observed often, vasospasm in the retina has been photographically documented in fewer than 10 patients (3-8). Vasospasm may occur as a primary event or secondary to other causes of transient monocular visual loss. It may be triggered by stress, cold, hypertension, hypotension, and low flow induced by the passage of embolic material. Winterkorn and Burde (9) published a photograph showing a narrowed artery proximal to a retinal embolus, which they attributed to vasospasm in reaction to irritation from passage of the embolus.

The notion that visual loss in the anterior visual pathway can be ascribed to migraine derives from the long-supplanted concept of migraine as a vasospastic process (10). According to the vasospastic theory of migraine, vasoconstriction explains the aura and vasodilation explains the subsequent headache. But the vasospastic paradigm cannot account for the details of blood flow during migraine (10). If migraine were a vasospastic process, its clinical manifestations would correlate in time with vasoconstriction and vasodilation of the cortical vessels, which they do not (10).

The hemodynamic changes that occur with migraine are not due to vasospasm but rather to changes in neuronal activity and platelet function (11). In migraine, oligemia occurs in multiple vascular territories in concert with a slowly spreading wave of cortical depression as described in animal models by Leão (12).

Thus, migraine affects the visual cortex and causes homonymous visual field loss. The pathophysiology of migraine would not explain monocular visual loss. Acknowledging the fact that patients often have difficulty discriminating homonymous from monocular visual loss, physicians' misapplication of the term "migraine" to a retinal mechanism confuses the issue further. In the retina, it is probably vasospasm, not migraine that causes unexplained transient monocular visual loss, especially in otherwise healthy young individuals (9).

The term "retinal migraine" is anatomically inconsistent, referring to a cortical process as though it were occurring in the retina. Unfortunately, the International Headache
Society (IHS) has defined "retinal migraine" as two attacks of fully reversible monocular visual loss associated with migraine headache. Grosberg et al (13) recently extended the definition to include patients with persistent monocular visual loss, hypothesizing that a migrainous process can cause persistent retinal damage—"an ocular form of migrainous infarction." Of course, migraine is so prevalent that it could occur in a patient who also has retinal vasospasm or retinal vascular occlusion. However, migraine is a different process occurring in a different location. The basis for migraine is neuronal instability rather than vascular instability. Indeed, the prevailing view articulated by Goadsby (11) is that migraine arises from changes in brainstem regions involved in sensory modulation. Patients with vasospastic conditions such as Raynaud digital symptom or Prinzmetal coronary angina may be susceptible to development of ocular vasospasm (6,9), and this suggests an underlying pathophysiology for vasospastic conditions. If only because migraine so rarely occurs together with these conditions, we should be looking for a different underlying cause for vasospasm.

In this issue of the Journal, Hill et al (14) apply strict IHS criteria in a broad-based review of the reported cases of transient monocular visual loss, finding that retinal migraine is, at best, exceedingly rare. Only 5 of 142 cases they reviewed qualify as definite retinal migraine under the IHS criteria. The authors attribute the other cases of transient monocular visual loss to retinal vasospasm.

Hill et al (14) have done a good job of helping to rehabilitate vasospasm as a cause of monocular visual loss. They argue that such visual loss is most often not accompanied by migrainous headache or aura. They point out that although cortical spreading depression is an attractive hypothesis for the pathophysiology of migraine, no clinical correlation has been made between retinal spreading depression and monocular visual loss. As the authors also remind us, spreading depression has been observed in vitro in the avascular retinas of frogs and chicks but has never been seen in vascularized mammalian retinas (14).

These are good arguments, but it is important to keep in mind the fact that retinal vasospasm remains a diagnosis of exclusion except in the very rare patient in whom it is caught in the act by ophthalmoscopy. It is especially important not to ascribe persistent visual loss to migraine but to pursue the cause, with migraine as one of the clues. A migraine diathesis may be a marker for an underlying defect such as hypertension, hypercoagulability, lupus cry-thematosus, or mitral valve prolapse and therefore might occasionally co-occur with vascular occlusion or retinal vasospasm. In diagnosing vasospasm, care should be taken to address these conditions, as well as optic disc drusen, smoking, and glaucoma. When vasospasm remains after other conditions are excluded, confirmatory treatment with calcium channel blockers may be indicated (6,15).

"Retinal migraine," with its cousins "ophthalmic migraine" and "ocular migraine," is an oxymoron. It is misleading and should not be part of the medical vocabulary.

REFERENCES
Most Cases Labeled as "Retinal Migraine" Are Not Migraine

Donna L. Hill, MD, Robert B. Daroff, MD, Anne Ducros, MD, PhD, Nancy J. Newman, MD, and Valérie Biousse, MD

Background: Monocular visual loss has often been labeled "retinal migraine." Yet there is reason to believe that many such cases do not meet the criteria set out by the International Headache Society (IHS), which defines "retinal migraine" as attacks of fully reversible monocular visual disturbance associated with migraine headache and a normal neuro-ophthalmic examination between attacks.

Methods: We performed a literature search of articles mentioning "retinal migraine," "anterior visual pathway migraine," "monocular migraine," "ocular migraine," "retinal vasospasm," "transient monocular visual loss," and "retinal spreading depression" using Medline and older textbooks. We applied the IHS criteria for retinal migraine to all cases so labeled. To be included as definite retinal migraine, patients were required to have had at least two episodes of transient monocular visual loss associated with, or followed by, a headache with migrainous features.

Results: Only 16 patients with transient monocular visual loss had clinical manifestations consistent with retinal migraine. Only 5 of these patients met the IHS criteria for definite retinal migraine. No patient with permanent visual loss met the IHS criteria for retinal migraine.

Conclusions: Definite retinal migraine, as defined by the IHS criteria, is an exceedingly rare cause of transient monocular visual loss. There are no convincing reports of permanent monocular visual loss associated with migraine. Most cases of transient monocular visual loss diagnosed as retinal migraine would more properly be diagnosed as "presumed retinal vasospasm."

After the development of the ophthalmoscope permitted visualization of the retina in vivo, Galezowski (1) observed retinal changes suggesting infarction in patients presenting with visual symptoms and presumed migraine headaches. Working with Charcot in Paris, Galezowski had heard Fére (2,3), one of Charcot’s residents, report that cerebral infarction may be related to migraine. Galezowski (4) hypothesized that a permanent "retinal or optic nerve affection," similar to changes described in the brain by Fére, could be secondary to migraine. In 1892, Galezowski (4) used the term "ophthalmic megrim" to describe permanent monocular visual loss associated with migraine headache. Subsequently, Fisher (5,6) in 1952 and 1971 and Walsh and Hoyt (7) in 1969 suggested that the eye itself can be affected by migraine.

In 1970, Carroll (8) introduced the term "retinal migraine" to describe 15 patients with transient and persistent monocular visual loss. None of the patients, however, had associated headaches. Authors have since used the term "retinal migraine" to describe a multitude of monocular visual symptoms, including events without associated headache and those resulting in permanent visual loss. Some authors have used other terms, including "anterior visual pathway migraine," "ocular migraine," "ophthalmic migraine," and "monocular migraine" (9-17).

In the original (1988) classification of headache, the International Headache Society (IHS) included "retinal migraine" as a subtype of migraine (18) and provided strict diagnostic criteria. These criteria stated that retinal migraine could be diagnosed only in the presence of fully reversible monocular visual disturbances associated with
typical migraine headache and with a normal neuro-ophthalmic examination between attacks. As with all forms of migraine, other causes had to be excluded. The revised 2004 IHS classification (19) also included retinal migraine. As in the 1988 classification, retinal migraine was considered sufficiently atypical as an aura that it was not classified under “migraine with aura” but listed as a separate entity (Table 1). The diagnostic criteria were unchanged (Table 2), again requiring “at least two attacks” of “fully reversible” monocular visual symptoms “associated with migraine headache” (Table 3).

Spreading depression (SD), as described by Leão (20) in 1944, is an excitation wave followed by depression of neuronal activity propagating through gray matter with a velocity of approximately 3 mm/min that investigators have observed in almost all gray matter regions of the central nervous system (21). Functional imaging and magnetoencephalographic studies strongly suggest that cortical SD constitutes the biological basis for the occipital aura that precedes headache in migraineurs (22,23). SD is often cited as the cause of retinal migraine.

We have reviewed the reported cases attributed to retinal migraine to determine whether they meet the strict criteria set out by the IHS.

METHODS

Using Medline and textbooks, we searched for articles mentioning “retinal migraine,” “anterior visual pathway migraine,” “ophthalmic migraine,” “ocular migraine,” “retinal vasospasm,” “transient monocular visual loss,” “visual loss and migraine,” “visual field defects in migraine,” and “retinal spreading depression.” Applying the most recent IHS criteria (Table 2) (19) for retinal migraine to all reported patients, we separated them into three categories: definite retinal migraine, probable retinal migraine, and possible retinal migraine (Table 4). Articles were not included in Table 4 if they lacked sufficient information for adequate classification. We also excluded patients with underlying diseases known to produce migraine-like symptoms, such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), antiphospholipid antibody syndrome, or systemic lupus erythematosus (24–27).

To be included as definite retinal migraine, the patients must have had at least two episodes of transient monocular visual loss associated with or followed by a migraine headache.

RESULTS

We discovered 60 articles describing 142 patients with transient or persistent visual symptoms attributed to retinal migraine.

<table>
<thead>
<tr>
<th>TABLE 1. Classification of migraine according to the International Headache Society criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Migraine without aura</td>
</tr>
<tr>
<td>1.2 Migraine with aura</td>
</tr>
<tr>
<td>1.2.1 Typical aura with migrane headache</td>
</tr>
<tr>
<td>1.2.2 Typical aura with non-migrane headache</td>
</tr>
<tr>
<td>1.2.3 Typical aura without headache</td>
</tr>
<tr>
<td>1.2.4 Familial hemiplegic migraine</td>
</tr>
<tr>
<td>1.2.5 Sporadic hemiplegic migraine</td>
</tr>
<tr>
<td>1.2.6 Basilar-type migraine</td>
</tr>
<tr>
<td>1.3 Childhood periodic syndromes that are commonly precursors of migraine</td>
</tr>
<tr>
<td>1.3.1 Cyclical vomiting</td>
</tr>
<tr>
<td>1.3.2 Abdominal migraine</td>
</tr>
<tr>
<td>1.3.3 Benign paroxysmal vertigo of childhood</td>
</tr>
<tr>
<td>1.4 Retinal migraine</td>
</tr>
<tr>
<td>1.5 Complications of migraine</td>
</tr>
<tr>
<td>1.5.1 Chronic migraine</td>
</tr>
<tr>
<td>1.5.2 Status migrainous</td>
</tr>
<tr>
<td>1.5.3 Persistent aura without infarction</td>
</tr>
<tr>
<td>1.5.4 Migrainous infarction</td>
</tr>
<tr>
<td>1.5.5 Migraine-triggered seizure</td>
</tr>
<tr>
<td>1.6 Probable migraine</td>
</tr>
<tr>
<td>1.6.1 Probable migraine without aura</td>
</tr>
<tr>
<td>1.6.2 Probable migraine with aura</td>
</tr>
<tr>
<td>1.6.3 Probable chronic migraine</td>
</tr>
</tbody>
</table>

Adapted from The International Classification of Headache Disorders, 2nd edition (19).

<table>
<thead>
<tr>
<th>TABLE 2. International Headache Society criteria for retinal migraine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description: Repeated attacks of monocular visual disturbance, including scintillations, scotomata, or blindness, associated with migraine headache</td>
</tr>
<tr>
<td>Diagnostic criteria:</td>
</tr>
<tr>
<td>A. At least two attacks fulfilling criteria B and C</td>
</tr>
<tr>
<td>B. Fully reversible monocular positive and/or negative visual phenomena (scintillations, scotomata, or blindness) confirmed by examination during an attack or (after proper instruction) by the patient's drawing of a monocular field defect during an attack</td>
</tr>
<tr>
<td>C. Headache, fulfilling criteria B–D for 1.1 Migraine without aura* begins during the visual symptoms or follows them within 60 minutes</td>
</tr>
<tr>
<td>D. Normal ophthalmologic examination between attacks</td>
</tr>
<tr>
<td>E. Not attributed to another disorder†</td>
</tr>
</tbody>
</table>

Adapted from The International Classification of Headache Disorders, 2nd edition (19).

*See Table 3.
†Other causes of transient monocular visual loss must be excluded.
Retinal Migraine

disorders (4-13,24-57). Among these 142 patients, 39 (from 25 articles) had visual loss (4,6-8, 11,25,27-45). Among these 39, there was central retinal artery occlusion in 11 (4,6,7,11,25,33,36,42), cilioretinal artery occlusion in 4 (38,43), branch retinal artery occlusion in 9 (31,35,37,39,43), focal retinal ischemia in 1 (32), central retinal vein occlusion in 2 (27,40), ischemic optic neuropathy in 6 (34,41,44), optic atrophy in 5 (4,28), and no explanation in 1 (6,45). Also among these 39 patients with persistent visual loss, 10 (4,6,7,27,31,32,33,34,45) initially presented with recurrent transient monocular visual loss associated with headaches consistent with presumed retinal migraine; these 10 patients developed permanent visual loss from 6 weeks to 20 years after the onset of transient visual loss.

Of the 103 patients with transient visual loss attributed to retinal migraine, only 16 had clinical manifestations that were actually consistent with retinal migraine (Table 4) (45-53). Among the many articles attributing transient monocular visual loss to retinal migraine (or equivalent terms for this condition), we found 12 patients with well-documented segmental retinal vasospasm of arteries or veins evident on ophthalmoscopy during an attack of transient monocular visual loss (7,13,56-63). Only 1 of these 12 patients had headache during or immediately after the visual loss (57), but the pain did not conform to IHS-defined migraine. Two of the patients had a history of migraine without aura (56,63), and one had previous episodes of cluster headache (13), but no headaches temporally associated with the monocular visual loss. The duration of visual loss varied from seconds to 4 hours, but most episodes lasted a few minutes. All but one patient (59) had only negative visual phenomena.

**DISCUSSION**

Our review indicates that retinal migraine, as currently defined in the IHS classification, is exceedingly rare. We acknowledge that a literature review can only approximate accuracy, because many reports had incomplete descriptions or were published before the 1988 IHS Headache Classification. In addition, not all patients with retinal migraine have been reported. The authors of this article have examined several patients with monocular visual loss who meet the criteria for a diagnosis of retinal migraine.

The typical visual aura of migraine occurs in a hemifield rather than a single eye, given that the aura originates from the occipital lobe (primary visual cortex) (64). Many patients report this visual experience as monocular (19,65,66), as they may attend only to the visual phenomena seen in the temporal field, perhaps because the temporal field is larger than the nasal field. Headache typically follows the aura, although there can be a migrainous aura without headache (18,19). Gradually expanding binocular scintillations, scotomas, and zig-zag lines (“scintillating scotoma” or “fortification scotoma”), with a duration usually between 5 and 20 minutes and not more than 60 minutes, are diagnostic of a migrainous visual aura (64,65,67), particularly if the aura is followed by headache. In 1971, Richards (67) attributed the zig-zag visual phenomena in the aura to the columnar organization of the visual cortex.

By contrast, monocular visual phenomena typically originate in the retina, choroid, or optic nerve (68). The positive visual phenomena are usually simpler than those that originate in the occipital lobe. They consist of phosphenes, flashing lights, flickering, or a “rain shower” (68-74). Because these visual manifestations may be caused by any process that impairs ocular or optic nerve blood flow, IHS criteria require that “other causes” be excluded before establishing migraine as the diagnosis (18,19,75).

The attribution of monocular visual loss to migraine is based on the concept of retinal SD, first described by Gouras (76) in 1958 in the frog retina. In 1966, Martins-Ferreira and de Castro (77) recorded similar changes in the
<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Age/ Gender</th>
<th>Number of episodes</th>
<th>Eye involved</th>
<th>Type of visual symptoms</th>
<th>Duration of visual symptoms</th>
<th>Headaches</th>
<th>Side of headache</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grosberg et al. (2006)</td>
<td>42/W</td>
<td>Multiple</td>
<td>OS</td>
<td>Positive and negative</td>
<td>7-8 minutes</td>
<td>Follow visual symptoms</td>
<td>NA</td>
</tr>
<tr>
<td>Grosberg et al. (2006)</td>
<td>35/M</td>
<td>Multiple</td>
<td>OS</td>
<td>Negative</td>
<td>5 minutes</td>
<td>Follow visual symptoms</td>
<td>Ipsilateral</td>
</tr>
<tr>
<td>Gan et al. (2005)</td>
<td>40/M</td>
<td>Multiple</td>
<td>Either</td>
<td>Negative</td>
<td>5-10 minutes</td>
<td>Follow visual symptoms</td>
<td>NA</td>
</tr>
<tr>
<td>Guidetti et al. (2005)</td>
<td>9/M</td>
<td>Multiple</td>
<td>OD</td>
<td>Negative</td>
<td>2-3 minutes</td>
<td>During or following visual symptoms</td>
<td>Bilateral</td>
</tr>
<tr>
<td>Lewinshtein et al. (2004)</td>
<td>12/W</td>
<td>Multiple</td>
<td>OD</td>
<td>Positive and negative</td>
<td>&lt;30 minutes</td>
<td>Follow visual symptoms</td>
<td>Ipsilateral</td>
</tr>
<tr>
<td>Lewinshtein et al. (2004)</td>
<td>13/M</td>
<td>Multiple</td>
<td>OD</td>
<td>Negative</td>
<td>3 minutes</td>
<td>No details</td>
<td>NA</td>
</tr>
<tr>
<td>Hachinski et al. (1973)</td>
<td>17/M</td>
<td>Multiple</td>
<td>Either</td>
<td>Positive and negative</td>
<td>15 minutes</td>
<td>No details</td>
<td>Ipsilateral</td>
</tr>
<tr>
<td>Joffe (1971)</td>
<td>18/M</td>
<td>Multiple</td>
<td>OD</td>
<td>Negative</td>
<td>NA</td>
<td>Some with binocular visual aura, Some without headache</td>
<td>Bilateral</td>
</tr>
<tr>
<td>Joffe (1971)</td>
<td>18/M</td>
<td>Multiple</td>
<td>Either</td>
<td>Negative</td>
<td>NA</td>
<td>Some with binocular visual aura</td>
<td>Bilateral</td>
</tr>
<tr>
<td>Joffe (1971)</td>
<td>34/M</td>
<td>Multiple</td>
<td>OS</td>
<td>Negative</td>
<td>NA</td>
<td>Some with binocular visual aura</td>
<td>Bilateral</td>
</tr>
<tr>
<td>Kupersmith et al. (1979)</td>
<td>53/W</td>
<td>2</td>
<td>OS</td>
<td>Negative</td>
<td>60 minutes</td>
<td>Some with binocular visual aura</td>
<td>Ipsilateral</td>
</tr>
<tr>
<td>Kupersmith et al. (1979)</td>
<td>21/M</td>
<td>2</td>
<td>OD</td>
<td>Negative</td>
<td>5 minutes</td>
<td>No details</td>
<td>NA</td>
</tr>
<tr>
<td>Kupersmith et al. (1987)</td>
<td>26/W</td>
<td>Multiple</td>
<td>OD</td>
<td>Negative</td>
<td>60 minutes</td>
<td>No details</td>
<td>Ipsilateral</td>
</tr>
<tr>
<td>Kupersmith et al. (1987)</td>
<td>16/W</td>
<td>Multiple</td>
<td>OD</td>
<td>Negative</td>
<td>NA</td>
<td>No details</td>
<td>Ipsilateral</td>
</tr>
<tr>
<td>Kupersmith et al. (1987)</td>
<td>28/W</td>
<td>Multiple</td>
<td>OS</td>
<td>Negative</td>
<td>20 minutes</td>
<td>Some with binocular visual aura</td>
<td>Bilateral</td>
</tr>
</tbody>
</table>

NA. Not available. Only patients with at least two episodes of transient monocular visual loss and headaches suggestive of migraine are included. None of these patients had permanent visual loss. Patients 1–5 had retinal migraine fulfilling IHS-IHCD2 criteria. We designated these patients as “definite retinal migraine.” Patients 6–7 had headaches that could not be diagnosed definitely as migraine, as defined by IHS-IHCD2. We designated these patients as “probable retinal migraine.” Patients 8–16 are reported in insufficient detail and so are designated “possible retinal migraine.” Most had migraine with binocular visual aura, as well as monocular episodes. Patient 6 had a nerve fiber layer infarct during an episode of transient monocular visual loss.

Optical signal during SD in the chick retina. This model of SD has since been extensively investigated in vitro, mostly on the chick retina (78). The technique involves removal of the eye from the animal, followed by separating the retina from the vitreous and placing the eyecup in buffered solution. Mechanical stimulation is applied to the periphery of the retina and a wave, similar to that described by Leão (20) propagates in a circular path through the whole tissue. This wave is accompanied by a reversible voltage shift that induces changes in the intrinsic optical properties of the tissue (20,23). Variations in light scattering allow the observer to visualize the circling wave as an enlarging dark circle invading the retinal tissue (Fig. 1) (77,78).

Retinal SD has only been demonstrated in vitro in avascular chick and frog retina. No in vivo models have demonstrated retinal SD, nor has it been demonstrated in any animal with retinal vasculature. The isolated retina in animal experiments is not representative of the human eye in vivo, which is vascularized and supported by the highly vascular choroid. SD would seem unlikely in the choroid, a blood-filled sponge, or optic nerve, where dysfunction generally produces visual loss and rarely simple...
phosphene. Although some of the monocular visual symptoms reported as retinal migraine progress and propagate at the same speed as cortical SD, retinal SD has never been demonstrated in mammals. Scientists studying retinal SD have never suggested any clinical correlation with migraine in humans.

Retinal vasospasm can produce transient monocular visual loss. However, in the vast majority of well-documented cases of retinal vasospasm, the clinical presentation is not suggestive of migraine. Only 1 of the 12 well-documented patients with ophthalmoscopically seen vasospasm uncovered in our search had headache during or immediately after the visual loss (57), and the pain did not conform to IHS-defined migraine. All but one of these patients (59) had only negative visual phenomena.

Based on our review, we find no basis for considering migraine to be the cause of permanent monocular visual loss unless the patient had previous transient monocular visual episodes consistent with IHS-defined retinal migraine. Two recent reviews suggesting that permanent monocular visual loss is present in up to 50% of patients with retinal migraine included patients who did not have IHS-defined retinal migraine before the visual loss (45,79). The various retinal lesions reported in presumed retinal migraine include central retinal artery occlusion, branch retinal artery occlusion, localized retinal ischemia, central retinal vein occlusion, and optic atrophy. These conditions cannot reasonably be explained by a single unifying mechanism such as SD. What authors have referred to as “retinal migraine” probably represents a large heterogeneous group of underlying disorders involving the retina, choroid, or optic nerve.

Based on our review, retinal migraine is unlikely to be the cause of transient or persistent monocular visual loss. Most reported cases attributed to this condition have not met strict IHS criteria. Moreover, there are no studies in humans to suggest that the retina is subject to SD, the process believed to underlie the binocular visual aura emanating from the visual cortex in migraine. We suggest that most patients reported to have had retinal migraine as the cause of transient monocular visual loss would be better labeled as having had “presumed retinal vasospasm (80).”

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Wall-Eyed Bilateral Internuclear Ophthalmoplegia From Lesions at Different Levels in the Brainstem

Chien-Ming Chen, MD and Sung-Hsiung Lin, MD

Abstract: Wall-eyed bilateral internuclear ophthalmoplegia (WEBINO) is a rarely reported syndrome. There is dispute about whether WEBINO is caused by a pontine or a midbrain lesion and whether the medial rectus subnuclei are implicated. In a study of the clinical and imaging features of four patients with WEBINO, we found that that three of four lesions involved the midbrain but not necessarily the medial rectus subnuclei.

CASE REPORTS

Case 1
A 66-year-old man with a 3 year history of systemic hypertension and diabetes mellitus presented with dizziness, unsteadiness, and double vision that had begun 2 days earlier. General physical and neurologic examinations were normal except for ocular motility.

In primary gaze position, both eyes were exodeviated, with the left eye being more so. On horizontal gaze, the abducting eye deviated fully, but the adducting eye did not cross the midline. Downgaze was intact, but upgaze and convergence were impaired. Pupils measured 4 mm in dim illumination and constricted normally to direct light. There was no ptosis (Fig. 1).

Brain MRI performed 4 days later disclosed a slit-like T2 hyperintense lesion in the paramedian midbrain that extended from the aqueduct dorsally almost to the interpeduncular cistern ventrally (Fig. 2A, B). The cause was presumed to be an infarct.

His dizziness and unsteadiness soon subsided. Eight weeks later, the upgaze impairment, exotropia, and left adduction deficit had disappeared. MRI performed 4 months after the onset, when the only clinical deficits were absent right adduction and convergence, showed that the lesion had become smaller (Fig. 2C, D). By 9 months after onset, the convergence deficit was gone, but the right adduction deficit lingered.

Case 2
An 84-year-old man with uncontrolled systemic hypertension developed acute mild left hemiparesis. He veered to the left on sitting and standing. No dysmetria was seen on finger-to-nose testing. Ocular motility examination showed mild bilateral exotropia, particularly on attempted upgaze. Bilateral adduction deficits were noted on horizontal gaze, together with nystagmus in the abducting eyes. Downgaze was normal, but upgaze and convergence were defective (Fig. 3). There was no ptosis and no facial or bulbar palsy, and the plantar responses were flexor bilaterally.

Brain MRI performed the following day revealed two hyperintense lesions on FLAIR and diffusion-weighted imaging (DWI), one at the dorsal pons-midbrain...
FIG. 1. Case 1: Ocular motility. Bilateral exodeviation is present in primary gaze position. Neither eye adducts on horizontal gaze. Downgaze is intact, but upgaze and convergence (bottom) are deficient.

FIG. 2. Case 1: Brain imaging. T2 axial (A) and coronal (B) MRI reveals a paramedian slit-like high signal abnormality almost bisecting the midbrain (arrow). Four months later, T2 axial (C) and coronal (D) MRI, when the patient had only a right internuclear ophthalmoplegia (INO) and a convergence deficit, shows persistence of the dorsal portion of the lesion near the aqueduct.
FIG. 3. Case 2: Ocular motility. The left eye is exodeviated in primary gaze position. There is no adduction of either eye on horizontal gaze. Downgaze is normal, but upgaze and convergence are defective.

junction abutting the fourth ventricle and extending into the right paramedian midbrain and the other in the right subcortical region (Fig. 4). The former lesion accounted for the ocular findings and the latter lesion for the mild left hemiparesis. He was determined to have had an ischemic stroke. Within 2 weeks, he had regained the ability to walk. Within 6 weeks, the left adduction and upgaze deficits and

FIG. 4. Case 2: Brain imaging. Axial FLAIR (A–C), axial diffusion-weighted (D, E), and T2 coronal (F) MRI show a hyperintense signal at the dorsal pons-midbrain junction bilaterally that extends to the right paramedian midbrain. There is also an unrelated signal abnormality in the right subcortical region.
exotropia had disappeared, but the right adduction and convergence deficits persisted.

Case 3
A 51-year-old schizophrenic woman suddenly developed vomiting and the inability to walk followed by altered consciousness over a 1 day period. She was stuporous with apparent incomplete right hemiparesis. Plantar responses were flexor bilaterally. When her eyelids were manually elevated, alternating exotropia was noted. Both eyes failed to cross the midline on oculocephalic maneuver (Fig. 5).

Brain CT scanning (Fig. 6A–C) disclosed an enhancing mass at the pons-midbrain junction with enlargement of the third and lateral ventricles. Ventriculoperitoneal shunting was performed immediately.

She gradually recovered consciousness. At 1 month after onset, she was able to cooperate with clinical eye movement testing. In primary gaze position, her left eye was exodeviated. On horizontal gaze, the right eye adducted 50% beyond the midline, and the left eye did not cross the midline. Both eyes abducted normally.

A brain CT scan performed immediately after shunting (Fig. 6D–F) clearly disclosed a mass extending through the midbrain into the third ventricle. An astrocytoma or oligodendroglioma was presumed, but pathologic confirmation was not obtained.

Case 4
A 65-year-old diabetic hypertensive woman developed acute dense right hemiplegia. Six weeks earlier, she had sustained a minor stroke with mild hemiplegia and hemisensory loss affecting the left limbs.

On our examination, she had a new right upper motor neuron facial palsy and a right extensor plantar response. Bilateral exodeviation of the eyes was noted in primary and downgaze, which was more prominent in the left eye. Neither eye crossed the midline on attempted horizontal gaze, and there was nystagmus in the abducting eye. Upgaze and downgaze were intact, but convergence was impaired (Fig. 7).

Emergency brain CT scanning disclosed a small right periventricular subcortical infarct that had probably occurred 6 weeks earlier. Brain MRI performed 5 days after new stroke onset (Fig. 8) disclosed a signal abnormality spreading over almost the entire rostrocaudal extent of the left pons, extending beyond the midline in the low to middle pons but sparing the paramedian brainstem rostral to the midpontine level. The neurologic deficits and ocular abnormality persisted. Nine months later, the patient died of hepatic cirrhosis, but no autopsy was obtained.

DISCUSSION
In our four cases of WEBINO, believed to be the largest with reported series accompanying MRI, three patients showed lesions involving the midbrain (Cases 1–3). Even in the three cases that involved the midbrain, the medial rectus subnuclei were not clearly involved.

Previous attempts to define the involvement of the medial rectus subnuclei have had flaws. Before CT brain imaging became available, Gonyea (4) located the lesion within the pons in one of three patients with WEBINO because of concurrent left peripheral facial weakness and right arm weakness. But as the patient also had a prominent right medial rectus palsy, the lesion might have extended into the midbrain.

Takamatsu and Ohta (5) described a patient with an initial left one-and-a-half syndrome (OHS) and paralytic pontine exotropia (PPE), evolving into WEBINO and later into right INO. T2 MRI showed high signal intensity lesions in the paramedian portion of the midpontine tegmentum bilaterally. The authors believed that the WEBINO was caused by a pontine lesion and that PPE, OHS, and WEBINO were reflections of the same lesion. However, the left OHS suggests involvement of the left MLF plus either the left paramedian pontine reticular formation (PPRF) or the left abducens nucleus or both structures (6–8).

Contralateral exotropia in PPE is attributed to involvement of the PPRF. The gaze deviation is due to the unopposed tonic activity of the spared PPRF on the side opposite to a unilateral lesion. If both sides of the pons were symmetrically damaged, exotropia would not occur (6,8,9).

If the lesions seen in the MRI were responsible for the unilateral exotropia of PPE as well as the bilateral exotropia in their case, there would have to be bilateral PPRF involvement. This conclusion is impossible, however, because supranuclear tonic ocular deviation via the PPRF would fail to induce exotropia bilaterally.

Strominger et al (10) reported a largely preserved oculomotor nucleus in necropsy material of a patient with WEBINO who died of metastatic small cell carcinoma and
who had had progressive right hemiplegia, right exotropia in primary gaze, bilateral adduction deficits, and impaired convergence. Complete demyelination was documented in both MLFs at the pons-midbrain junction. The oculomotor complex showed only slight degenerative changes. However, the lesion did extend to the caudal midbrain. Given that medial rectus subgroup neurons are scattered within the MLF (see below), these neurons could have been affected in that patient.

**FIG. 6.** Case 3: Brain imaging. Brain CT scanning (A–C) discloses a pons-midbrain mass obstructing the aqueduct and enlarging the ventricles. Immediately after ventriculoperitoneal shunting 4 days later, a repeat CT scan (C–F) shows more clearly that the lesion extends through the midbrain into the third ventricle.

**FIG 7.** Case 4: Ocular motility. The left eye is exodeviated in primary gaze position. There is no adduction of either eye on horizontal gaze. Vertical gaze is normal, but convergence (bottom) is deficient.
Another contradiction to the concept of medial rectus subnucleus involvement in WEBINO has come from the observations that exotropia also occurs ipsilaterally in unilateral INO, that is, in the wall-eyed monocular INO (WEMINO) syndrome. Among four patients with WEMINO described by Johnston and Sharpe (11), pathologic analysis obtained for one patient showed that the lesion was confined to the pontine tegmentum. However, the authors did not specify whether the exotropia was ipsilateral or contralateral.

Ikeda and Okamoto (12) reported a case of left WEMINO with a tiny MRI lesion in the left paramedian pontine tegmentum just adjacent to the fourth ventricle. However, this patient also had bilateral upbeat nystagmus and convergence deficiency, suggesting that the lesion might have extended into the midbrain.

Recent anatomic studies (13–15) are pertinent to the analysis of structure-function relationships in WEBINO. The oculomotor nuclear complex is a slanted structure with its ventral part pointing upward. The MLF passes just lateral and inferior to it. Of the medial rectus motoneurons, three subgroups can be identified. The first subgroup lies in the most ventral portion of the oculomotor complex. The second subgroup lies in the dorsal portion at the caudal level. The third subgroup, medial to the second, probably contains the medial rectus motoneurons responsible for convergence (subgroup C of Buttner-Ennever et al) (13). Studies of Aktekin et al (14) and Glicksman (15) have shown that there are medial rectus subgroup neurons scattered within the MLF.

Our Case 1 had WEBINO with impaired upgaze and convergence, evolving into a right INO with impaired convergence. MRI showed lesions in the paramedian midbrain, implying involvement of the medial rectus subnuclei along with the MLFs. The lesion in the first MRI looked like the midbrain cleft in a patient with WEBINO reported by Lagreze et al (16). Our Case 2 had a lesion at the pons-midbrain junction and right paramedian midbrain, where the possibility of medial rectus subnucleus involvement by edema or compression cannot be excluded. Our Case 3 also had a lesion extending through the midbrain into the third ventricle. In our Case 4, the lesion did not appear on MRI to reach the midbrain, but the patient clearly had convergence insufficiency. We acknowledge that convergence insufficiency may be seen in elderly persons and with cerebral lesions (the patient had a right subcortical infarct), but it may also indicate that the lesion involved the midbrain.

There is evidence from electro-oculographic studies that medial rectus subnucleus involvement is not necessary for exotropia. In two patients with WEBINO, Korniyama et al (17) demonstrated that deprivation of visual fixation with Frenzel goggles and eye closure diminished exotropia,
whereas one-eye fixation elicited marked outward deviation of the other eye. Conversely, a milder outward deviation of the eye on the INO side was noted during eye closure in three of seven patients with nonparalytic pontine exotropia (NPPE, contralateral exotropia with INO). These findings imply that the exotropia in WEBINO and NPPE depends on whether the PPRF contralateral to the damaged MLF participates in the secondary deviation under fixation with the paretic eye(s).

Johkura et al (18) described interesting ocular motor findings in four patients with OHS. All had mild outward deviation in both eyes with fixation prevented by Frenzel goggles. In three patients, the outward eye deviation was greater on the ipsilateral side and a transition from OHS to ipsilateral INO was noted, whereas a transition to ipsilateral gaze palsy was seen in the one patient whose deviation was greater on the contralateral side. These findings suggest that the eyes tend to be in divergent positions when fixation is prevented in OHS. Ipsilateral eye deviation is the result of MLF involvement and contralateral eye deviation is the result of PPRF involvement. The authors suggested that outward deviation of the ipsilateral eye is due to an imbalance of vestibular signals destined for the ipsilateral medial rectus in the MLF and that the outward deviation of the contralateral eye is due to an imbalance of PPRF signals.

Drawing an analogy to the theory of Brandt and Dieterich (19,20) that the ocular tilt reaction (skew torsion and head tilt) reflects imbalance of vestibular signals in the roll plane, ipsilateral exotropia may result from imbalance in the yaw plane in disorders involving the MLF. Ipsilateral exotropia may also occur in WEBINO or OHS. MLF axons carry signals from both PPRF and vestibular nuclei. Thus, WEBINO probably represents a bilateral form of NPPE, except that it is not necessarily pontine, and it is not likely to be a bilateral form of WEMINO. The presence of up-gaze palsy, as in our Cases 1 and 2, suggests that the lesion reaches into the midbrain.

REFERENCES
Optic Neuropathy Associated With Periostitis in Relapsing Polychondritis

Parima Hirunwiwatkul, MD and Jonathan D. Trobe, MD

Abstract: Optic neuropathy is an uncommon manifestation of relapsing polychondritis (RPC), a rare systemic disease affecting cartilaginous and proteoglycan-rich structures. The optic neuropathy has been attributed to ischemia, intrinsic inflammation of the optic nerve, or spread of inflammation to the nerve from adjacent intraconal orbital tissues. We report a case of recurrent corticosteroid-responsive optic neuropathy in which MRI did not show ocular, optic nerve, or intraconal orbital abnormalities but did show periosteal thickening and enhancement in the apical orbit and adjacent intracranial space consistent with periostitis. The periostitis, which is a manifestation of a systemic vasculitis or an autoimmune reaction to progenitors of cartilage, probably caused the optic neuropathy by compression or inflammation. It is important to recognize this mechanism of optic neuropathy as its imaging features may be a subtle yet critical clue to an underlying systemic condition that can be life-threatening if not properly managed.

(Relapsing polychondritis (RPC) is a rare multisystem disease affecting cartilaginous tissue and proteoglycan-rich structures such as the eye, heart, blood vessels, and inner ear (1). Several reports support autoimmunity to collagen types II, IX, and XI and other cartilaginous protein (2,3). In RPC, the major causes of death are pulmonary infection and respiratory collapse, renal failure, and cardiac valvular complications (1,4). Common ophthalmic manifestations include conjunctivitis, episcleritis, uveitis, and scleritis. Inflammatory orbitopathy and optic neuropathy have been reported rarely (5). The mechanism of optic neuropathy is believed to be ischemia, intrinsic inflammation of the optic nerve, or spread of inflammation from adjacent intraconal orbital tissues.

CASE REPORT

A 78-year-old woman had new onset of acute painless visual loss in the left eye. She denied fever, jaw claudication, weight loss, muscle pain, joint pain, or lethargy. However, she had had six bouts of redness, pain, and tenderness of either ear and of the dorsum of her feet over the past 4 years. Her primary care physician attributed the ear and foot lesions to granuloma annulare, a benign papular skin eruption that does not, however, involve the ear. Each episode would resolve within days after treatment with 10–20 mg prednisone daily. There was also a history of chronic hypertension for which she had been treated with a combination of hydrochlorothiazide and bisoprolol.

Examination elsewhere disclosed a best-corrected visual acuity of 20/25 in the right eye and 20/70 in the left eye. An afferent pupillary defect was present in the left eye with a swollen left optic disc. Humphrey visual fields showed nerve fiber bundle defects in both eyes with mean deviations of —5.6 db and —5.8 db. The rest of the ophthalmic examination was reported as normal.

An erythrocyte sedimentation rate (ESR) was 60 mm/h. A temporal artery biopsy was negative. She received a diagnosis of optic neuritis in the left eye of uncertain cause and was treated with 60 mg prednisone daily over 2 weeks. Visual acuity dramatically improved within 3 days of starting treatment and was recorded at 20/25 in both eyes 1 month later with resolution of optic disc edema in the left eye.

Three months later, she complained of left periocular pain and diminished vision in the left eye. Visual acuity was recorded as 20/30 in the right eye and 20/100 in the left eye. The left optic disc was reported to be slightly swollen again. She was diagnosed with recurrent optic neuritis and retreated with 60 mg oral prednisone daily. Within days she noted visual improvement. Visual acuity was recorded.
Optic Neuropathy in Relapsing Polychondritis

FIG. 1. A, B. Midorbital T1 coronal MRI. Comparison of precontrast (A) and postcontrast (B) studies shows no enhancement of the optic nerves. C, D. Orbital apex T1 coronal MRI. Comparison of the precontrast (C) and postcontrast (D) studies shows enhancement of the thickened periosteum of the orbital apices and adjacent intracranial meninges, which is greater on the left (arrows). The left optic nerve may be compressed by the thickened periosteum.

as 20/30 in both eyes 3 days after treatment was started. Two weeks after treatment was started, ESR was 26 mm/h.

Our examination 1 week later revealed a best-corrected visual acuity of 20/20 in both eyes. Visual fields showed mean deviations of −0.67 db and −1.72 db with scattered high threshold points but no obvious nerve fiber bundle defects. Pupils were normal in size and reactivity and displayed no afferent defect. The right optic disc was normal, but the left optic disc still showed mild swelling. There were no other neurologic deficits and no evidence of inflammation of her ears or feet.

Brain and orbit MRI showed enhancement and thickening of the periosteum within the orbital apices and the adjacent intracranial meninges, especially on the left side (Fig. 1). There was no thickening or enhancement of either optic nerve or other intracranial abnormalities.

Standard laboratory studies for an inflammatory disorder, including angiotensin-converting enzyme (ACE), antinuclear antibodies (ANA), dilute Russell viper venom, and coarse granular antineutrophil cytoplasmic antibodies (c-ANCA), were negative. The only positive test was perinuclear antineutrophil cytoplasmic antibodies (p-ANCA).

FIG. 2. A. The right ear is red and swollen during a relapse of polychondritis. B. The left ear is normal.
<table>
<thead>
<tr>
<th>Author</th>
<th>Number of cases</th>
<th>Author’s diagnosis</th>
<th>Other ophthalmic findings in affected eye</th>
<th>Other systemic diseases</th>
<th>Comment about mechanism of optic neuropathy</th>
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<tr>
<td>1. Ischemic mechanism</td>
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<td></td>
</tr>
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<td>Ischemic optic neuritis</td>
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<td>None</td>
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<td>Killian et al, 1978</td>
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<td>Nonarteritic ischemic optic neuropathy</td>
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<td>Isaak et al, 1986</td>
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<td>None</td>
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<td>2. Inflammatory/infiltrative mechanism</td>
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<td>Kaye et al, 1964</td>
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<td>Optic neuritis</td>
<td>Episcleritis, keratoconjunctivitis, keratitis</td>
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<td>Anderson, 1967</td>
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<td>McKay et al, 1974</td>
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<td>Isaak et al, 1986</td>
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<td>Pazirandeh et al, 1988</td>
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<td>Uveitis</td>
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<td>Tanaka et al, 1990</td>
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<td>Tucker et al, 1993</td>
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<td>Chronic orbital inflammation with lymphoid hyperplasia</td>
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<td>Lichaoco et al, 2001</td>
<td>1</td>
<td>Mucosa-associated lymphoid tissue (MALT) ± type B cell lymphoma</td>
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<td>3. Indeterminate mechanism</td>
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<td>Eckardt, 1981</td>
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<td>Bilateral optic atrophy</td>
<td>Paralysis of the extraocular muscles</td>
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TABLE 1. (Continued)

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<thead>
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<td>Isaak et al, 1986</td>
<td>4</td>
<td>Papilledema</td>
<td>NA</td>
<td>None</td>
<td>Not supported by clinical information such as intracranial pressure measurement</td>
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<td>Bilateral optic disc edema</td>
<td>Conjunctivitis, episcleritis</td>
<td>Cerebral vasculitis</td>
<td>May be inflammatory as patient responded to corticosteroid treatment and had cerebral vasculitis</td>
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NA, Not available.

CT scans of the abdomen and pelvis were negative. An echocardiogram showed minimal mitral, tricuspid, and pulmonic regurgitation accompanied by pulmonary hypertension. Chest x-ray was normal, but CT scanning of the chest showed multiple lung nodules. Bronchoscopic biopsy revealed fragments of bronchial wall with thick sclerotic vessels consistent with pulmonary hypertension.

Visual function remained unchanged without treatment during a follow-up period of 8 months. Repeat MRI performed 1 month and 5 months after our first consultation showed no change. However, she developed recurrent inflammation (Fig. 2) affecting either the right or left ear but sparing the earlobe that always resolved within days after treatment with 10–20 mg prednisone daily for 1 week. A presumptive diagnosis of RPC was made.

DISCUSSION

Our patient with RPC displayed recurrent unilateral optic neuropathy that appeared to be responsive to oral corticosteroid treatment. There were no clinical or imaging signs of inflammation of the eyes or intraconal orbital tissues. MRI showed thickening and enhancement of the apical periorbita and adjacent intracranial meninges, probably reflecting inflammation. We presume that the recurrent optic neuropathy was caused by compression of the apical optic nerve or inflammation of its dural covering. Neither intracranial dural nor periosteal inflammation has been described in RPC.

There have been 25 reported cases of optic neuropathy in RPC, 12 of which are derived from one review of ophthalmic manifestations of RPC and 13 from other single or double case reports (3,6–18). The optic neuropathy has been labeled as “optic neuritis” (ON), “anterior ischemic optic neuropathy” (AION), or “papilledema.” Although most reports do not provide enough detail to ascertain the precise mechanism, it has been presumed to be inflammatory (ON) if the vision improved with anti-inflammatory treatment and ischemic if it did not (Table 1).

Based on our review of reported case material for which there is enough detail, we would designate 4 cases as ischemic, 13 as inflammatory, and 8 of indeterminate mechanism. Imaging was available in only 2 cases. In one of these, CT scanning showed attenuation of orbital fat signal and intraconal biopsy-proven lymphoid hyperplasia (13); in the other, biopsy-proven mucosa-associated lymphoid tissue (MALT) (14) appeared to deform and perhaps infiltrate the optic nerve.

To our knowledge, the periosteal inflammation (“periostitis”) seen in our patient has not been reported.
in RPC, but it has been reported in other connective tissue or vascular disorders such as polyarteritis nodosa (19,20), sarcoidosis (21), and lupus erythematosus (22,23). In these disorders, vaso-occlusion is believed to cause hypoxia with release of bone-derived growth factors that induce inflammation of the periosteum (20).

Why might the periosteum be a target in RPC? Vaso-occlusion may result from immune complex attachment, as occurs in several vessels in RPC (16). Another possible mechanism is an autoimmune reaction to damaged periosteum, which has been reported to contain collagen type II, a minor component of the dura mater (24,25). The chondrogenic layer of the periosteum contains chondrocyte precursor cells that form cartilage during limb development and growth in utero and does so again in injured periosteum during fracture healing (26–28).

A third possible mechanism for periostitis in RPC is a limited form of pachymeningitis. Focal pachymeningitis has not been described in RPC, but there have been reports of what seems to be leptomeningeal involvement as part of “aseptic meningitis” (29–32), “migratory leptomeningeal inflammation” (33), and “meningocerebralitis” (34,35). These manifestations may be part of an autoimmune reaction to collagen type II, a minor component of the dura and notochord remnants (36). Moreover, pachymeningitis is reported in conditions similar to RPC, including rheumatoid arthritis (37–39), Wegener granulomatosis (WG) (40,41), and p-ANCA-positive microscopic polyangiitis (42–46). Indeed, WG (47,48), ankylosing spondylitis (49), lupus (50), and Behçet disease (51) have been reported to manifest anicular chondritis.

Given that we did not obtain tissue, did our patient actually have RPC or one of these other autoimmune disorders? We believe our diagnosis of RPC is justified on the basis of the modified McAdam criteria, which specify the presence of chondritis at two or more separate anatomic locations with response to corticosteroids or dapsone (52–54). She also had mitral valve regurgitation, which has been reported in RPC (55,56). Finally, there was no serologic support for WG or alternative diseases.

In conclusion, our patient showed a previously undocumented mechanism of optic neuropathy. Recognizing this mechanism is important for two reasons: 1) orbitocranial imaging features may be subtle, and 2) the diagnosis of RPC is critical because its effects on other cartilaginous and proteoglycan tissues may be life-threatening if not properly managed.

REFERENCES


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Hirunwitat and Trobe


Ocular Motor Disorders in Mitochondrial Encephalopathy With Lactic Acid and Stroke-Like Episodes With the 3271 (T-C) Point Mutation in Mitochondrial DNA

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Background: Ocular motor function can provide insights into areas of dysfunction within the nervous system. There are no published eye movement recordings in patients with mitochondrial encephalopathy with lactic acid and stroke-like episodes (MELAS). Our purpose in this study was to analyze the ocular motor features of a family with MELAS with a (T-C) mutation at nucleotide position 3271 in the mitochondrial tRNA-Leu gene.

Methods: The search coil method was used to record visually-guided saccades, antisaccades, and triangular pursuit tasks in the horizontal and vertical planes in three patients in a Japanese family with MELAS.

Results: The patients showed saccadic dysmetria and prolonged saccadic reaction times, deficits in the ability to suppress reflex eye movements, and increased reaction time during antisaccades, downbeat nystagmus, square wave jerks, and impairment in pursuit.

Conclusions: On the basis of eye movement recordings, patients with MELAS have frontal cortex as well as cerebellar dysfunction.

(Mitochondrial encephalomyopathy is based on biochemical and morphologic abnormalities of the mitochondria in association with mitochondrial DNA (mtDNA) mutations (1,2). It presents clinically as involvement of the central nervous system (CNS) as well as the skeletal muscle system because these organs require high levels of energy produced in the mitochondria (3). The clinically well-defined forms of the disease are classified as mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) (4), myoclonus epilepsy with ragged-red fibers (MERRF) (5), and Kearns-Sayre syndrome (6).

The 3243 mutation is found in 80% of patients with MELAS, and the 3271 mutation is the second most commonly reported type in MELAS, present at a frequency of 7%-15% (7,8). Although more than 10 mtDNA mutations have been reported in MELAS, the clinical features are grossly identical. Ocular changes in MELAS have included reversible scotoma, ophthalmoplegia, and pigmentary retinopathy (9,10).

We studied eye movements in three members of a Japanese family with MELAS with the 3271 (T-C) point mutation in mitochondrial DNA. We examined visually guided saccades, antisaccades, and pursuit to investigate cortical, subcortical, and cerebellar function. To our knowledge, there have been no previous reports on eye movement defects in patients with MELAS.

METHODS

Patients

The pedigree and the clinical features of our Japanese family have been reported previously (11). Three members in two generations of the family were examined for eye movements: the mother (Case 1), the older son (Case 2), and the younger son (Case 3). Systemic neurologic findings included cerebellar ataxia, dysarthria, tremor/myoclonus,
slight dementia with memory loss, and photogenic epilepsy, which were reasonably similar in severity in the three family members except for dementia, which was present only in Case 1 (Table 1). Case 1 presented with the inability to walk; the patient used a wheelchair. Case 2 showed shaky walking using a cane. Case 3 could walk. All patients had sufficient intelligence to understand our tasks.

Ophthalmic examinations revealed that all subjects had good visual acuity and no abnormalities of ocular fundi. Their visual fields were normal on Goldmann perimetry. No blepharoptosis or paresis of the extraocular muscles was observed. Brain MRI was normal in each patient. Lactate and pyruvate levels in serum and cerebrospinal fluid (CSF) were elevated in each case. Biopsy of the biceps brachii muscle showed ragged-red fibers; mtDNA analysis revealed a heteroplasmic (T-C) point mutation at position 3271 in the mitochondrial tRNA-Leu gene (UUR) (12) in each patient.

Six age-matched healthy subjects (mean age = 30.5 years, SD = 10.7, four men) served as control subjects. The study was approved by our institutional human subjects committee and followed the tenets of the Declaration of Helsinki. All subjects gave their informed consent for genetic testing and ophthalmic examinations.

Eye Movement Recording Equipment

Eye movements were measured three dimensionally with two orthogonal magnetic fields (the side length of cubic field coils was 89 cm) and a double-loop search coil (Skalar Medical, Delft, the Netherlands) on the right eye (13), and data were digitized at 1000 Hz. The double-loop search coil was calibrated by monitoring on a protractor device that could be rotated in horizontal, vertical, and torsional planes (in vitro calibration). Each subject sat upright in a chair with his or her head fixed with a bite bar at the center of the cubic field coils. We then carefully checked voltage offsets of the coil signals during each interval between recording sessions and compensated for them if necessary (in vivo calibration).

Testing Paradigms

Visually Guided Saccades

Nine light-emitting diodes (LEDs) 0.2° in diameter aligned horizontally and vertically at intervals of 10° on a tangent board were used for visually guided saccades. Subjects were instructed to look at a target moving in a stepwise manner from a fixation point to an eccentric point with amplitudes of 10 and 20° in horizontal and vertical planes. The target was turned on for 2-5 seconds at random, with the target lit as soon as the other target was extinguished. This task was carried out more than 40 times.

Antisaccades

In this task, the visual target was presented in the same manner as in the visually guided saccade task. Subjects were instructed to make a horizontal saccade to an imaginary point opposite to the side of the visual target presented in the peripheral field. We provided detailed preparatory explanation for this task.

Pursuit

A laser projector was used to present a target spot of 0.2° in diameter on the screen for the smooth pursuit task. The target was presented between 4 and 20°/s with an amplitude of ±20° in a triangular waveform pattern (4-6 cycles). Pursuit responses were tested in the horizontal and vertical planes to calculate steady-state pursuit gain (eye velocity divided by target velocity) during tracking of the target.

Data Analysis

Two components of eye position traces (vertical and horizontal) were displayed on a computer display for visual inspection, and periods with blinks were discarded. The onset of saccades was identified by an interactive computer program with velocity and acceleration criteria (velocity >40/s, acceleration >1,200/s²). Saccadic reaction time was calculated by subtracting the eye movement onset from target onset. Pursuit gain during triangular constant velocity waveform tracking was based on the average eye velocity after removal of saccades. The results were examined for
statistical significance by analysis of variance (ANOVA) and the Tukey-Kramer test.

RESULTS

Visually Guided Saccades

Saccades in all three patients showed abnormalities even on the simplest paradigm of visually guided saccades (Fig. 1). The reaction times and saccadic gains are shown in Fig. 2. The reaction times of saccades in all three patients were significantly prolonged compared with those of control subjects in each direction ($P < 0.01$) (Fig. 2A). Furthermore, the reaction times of downward saccades in Case 1 were significantly longer than those in Cases 2 and 3 ($P < 0.01$). Visually guided saccades were also characterized by dysmetria (Fig. 1). The primary saccades were dysmetric, falling short of the visual target in both horizontal and vertical planes and were followed by corrective saccades with reaction times that ranged from 149 to 307 ms. The gains of 10° saccades are shown in Fig. 2B. Hypermetric saccades (gain $>110\%$) occurred frequently in Case 1 (Fig. 1A) appearing in 50% of rightward, 100% of leftward, 17% of upward, and 67% of downward saccades. On the other hand, the majority of visually guided saccades in Case 2 (Fig. 1B) and Case 3 (Fig. 1C) were hypometric (gain $<90\%$). Saccadic velocities were normal in all patients.

Antisaccades

The error rates and reaction times for the normal control subjects were similar to those reported previously (15). On the other hand, two major deficits were observed during performance of the antisaccade paradigm in all patients (Table 2). The patients had a tendency to make a saccade (prosaccade) to the visual target although they were instructed to execute a saccade in the direction opposite to the visual target presented in the peripheral field. The inappropriate prosaccade was followed by an appropriate antisaccade in each trial (Fig. 3). These corrective saccades indicated that the patients understood the antisaccade task. These reflexive saccade reaction times were also significantly longer than those in control subjects ($P < 0.01$). The error rates indicated that the ability to suppress a prosaccade to the visual target was severely impaired in the three patients with MELAS.

Pursuit

Downward smooth pursuit showed low gain with interruption of catch-up saccades (Fig. 4). These average gains in the patients were low for all directions and decreased with increases in target velocity (Table 3). In contrast, the pursuit gains in control subjects were almost 1 for all directions when target speed was lower than 12°/s.

FIG. 1. Trajectories of leftward visually guided saccades in our three patients with MELAS. Every three saccades to visual target shifts of 10 and 20° are superimposed with alignment of target onset. Note that saccades in Cases 2 and 3 are hypometric, whereas those in Case 1 are hypermetric. R, right; L, left.
The gains for downward pursuit were clearly different from those for upward pursuit in each patient. There were no significant differences between rightward and leftward movements at the same velocity \((P > 0.05)\).

Downbeat nystagmus and square wave jerks frequently contaminated fixation and pursuit eye movements in Cases 1 and 2. The frequency and amplitude of the abnormal eye movements were larger in Case 1 than in Case 2. Amplitudes of fast-phase eye movements in downbeat nystagmus during fixation with the front target in the dark for Cases 1 and 2 averaged 2.2 ± 0.6 and 1.3 ± 0.3°, respectively. Slow-phase velocities averaged 1.4 ± 0.12°/s in Case 1 and 0.49 ± 0.09°/s in Case 2. Square wave jerks had average amplitudes of 0.95 ± 0.43° and average frequencies of 1.3 ± 0.27 Hz in Case 1 and 0.71 ± 0.27 and 1.0 ± 0.26 Hz in Case 2. On the other hand, neither downbeat nystagmus nor square wave jerks were observed in Case 3.

**DISCUSSION**

The present study demonstrated identical abnormalities of ocular motor function in three members of a family with MELAS associated with a mutation at nucleotide position 3271.

Two abnormal parameters in the saccades were observed consistently even in a simple task to generate visually guided saccades. The reaction times of saccades to a visual target presented in the peripheral field were significantly prolonged in both horizontal and vertical directions compared with those of normal control subjects, particularly in Case 1 in whom reaction times of up to more than 300 ms were observed in all directions. The saccade amplitude-maximum saccade velocity relationships for all three patients...
Another affected parameter was saccadic accuracy. Visually guided saccades were dysmetric for all directions. Most of the dysmetric saccades were hypometric and were followed by single or a few corrective saccades with intersaccadic intervals ranging from 140 to 307 ms. Hypometric saccades are common in subjects with cerebellar dysfunction (16).

A striking ocular motor deficit in these patients was observed in the antisaccade task. All three patients had difficulty suppressing reflexive saccades to the visual target. The frequency of directional error was greatest in Case 1, with an error rate of 90.3%. An appropriate antisaccade occurred only three times in a sequential trial, in which reaction times exhibited a large degree of scatter. Moreover, the percentages of errors were 81.6% in Case 2 and 53.1% in Case 3. These results suggested that the frequency of directional error became higher as the disease progressed. Even in Case 3, a 20-year-old patient with minimal neurologic manifestations, errors were observed in about half of the trials.

The antisaccade task requires the subject to suppress reflexive or anticipatory saccades toward the target. The potential sources of such suppression are the frontal eye fields (FEFs) and the supplementary eye fields (SEFs) (16). A recent animal study demonstrated that the majority of
MELAS

FIG. 4. Representative observations of vertical smooth pursuit eye movements at target velocities of 16, 8, and 4°/s in Case 2. Downward pursuit shows low gain with interruption by catch-up saccades. The upper trace, indicated by a solid line, shows vertical eye movements. The lower trace, indicated by a dotted line, shows target movement with amplitude of ±20°. The entire time scale is 10 seconds.

eye movement-related neurons in SEFs fired significantly more preceding antisaccades than prosaccades (17). Similar defects in generating antisaccades have been reported in patients with schizophrenia (18), Parkinson disease (19), Huntington disease (20), progressive supranuclear palsy (21), and Alzheimer disease (22).

All three patients also showed low gain pursuit. Cases 1 and 2 exhibited downbeat nystagmus. A vertical vestibular tone asymmetry, a neural integrator failure, and an imbalance of vertical smooth-pursuit signals have been proposed as mechanisms of downbeat nystagmus (23-25). Zee et al (25) proposed a model based on asymmetric vertical pursuit signals, in which the overbalance of upward visual velocity commands results in spontaneous upward drift. In a recent healthy human study, Marti et al (26) reported that vertical pursuit imbalance led to downbeat nystagmus in darkness. In our study, the minimal slow-phase velocities (1.4 ± 0.12 and 0.49 ± 0.09°/s) were not sufficient to cause the lower downward pursuit gains in Cases 1 and 2. A large asymmetry in vertical gains has been proposed as a possible mechanism for downbeat nystagmus (25). However, this hypothesis cannot apply to our Case 3. The assumption of an asymmetry of vertical pursuit signals is based on the observation of the tracking behavior of patients with cerebellar disease, who show relatively smooth upward but saccadic downward tracking during pursuit stimulation. Our results suggest that downward pursuit with low gain and downbeat nystagmus may be caused by effects on cerebellar control, given that cerebellar ataxia was observed in all three of our patients.

Acknowledgments
We thank Dr. D. A. Suzuki and Dr. K. Fukushima for valuable comments on the manuscript.

<table>
<thead>
<tr>
<th>TABLE 3. Eye velocity gains during smooth pursuit at each target speed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target velocity</strong></td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>Case 1</td>
</tr>
<tr>
<td>4°/s</td>
</tr>
<tr>
<td>8°/s</td>
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<tr>
<td>12°/s</td>
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<tr>
<td>Case 2</td>
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<td>4°/s</td>
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<td>8°/s</td>
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<td>20°/s</td>
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<tr>
<td>Case 3</td>
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<td>4°/s</td>
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<tr>
<td>8°/s</td>
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<tr>
<td>12°/s</td>
</tr>
<tr>
<td>20°/s</td>
</tr>
<tr>
<td>Control subjects</td>
</tr>
<tr>
<td>4°/s</td>
</tr>
<tr>
<td>8°/s</td>
</tr>
<tr>
<td>12°/s</td>
</tr>
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<td>20°/s</td>
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</table>

The gain is the velocity of eye movement divided by the velocity of the target. Values are means ± SD.
*P < 0.01, compared with control subjects.
REFERENCES


Painful Sixth Cranial Nerve Palsy Caused by a Malignant Trigeminal Nerve Sheath Tumor

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Abstract: A 17-year-old woman developed a sixth cranial nerve palsy from a malignant peripheral nerve sheath tumor of the trigeminal nerve. This case is unusual in that the principal symptom was diplopia stemming from a sixth cranial nerve palsy. Pain was mild, and trigeminal function was preserved. Imaging evidence of rapid growth of the cavernous sinus mass gave rise to an initial impression that the cause might be inflammatory. Treatment with gamma knife stereotactic radiosurgery produced some improvement in sixth cranial nerve function and reduction in tumor size over a follow-up period of 9 months.


Malignant peripheral nerve sheath tumors (MPNSTs) that involve the cranial nerves most often affect the trigeminal nerve (1–8) and present clinically with burning facial pain (2,8). We describe a patient with a biopsy-proven MPNST who presented with a sixth cranial nerve palsy, relatively mild facial pain, and preservation of trigeminal function. Imaging evidence of rapid tumor growth gave rise to the impression of an inflammatory cavernous sinus lesion or a metastatic or hematologic malignancy.

CASE REPORT

A 17-year-old woman developed sudden persistent horizontal diplopia 2 months before our initial evaluation. She also complained of occasional daily sharp pain of varying intensity over the left brow area, especially when she looked at a blackboard at school. She also noted some pain with extraocular movements but had no facial weakness or paresthesias. At the onset of diplopia, she had a throat and right ear infection treated with amoxicillin.

She reported monthly headaches with photophobia, phonophobia, nausea, and vomiting. Her last headache had occurred 4 months before her initial presentation. She also had a history of asthma and recurrent sinusitis. Medications included fluoxetine and amphetamine for attention deficit disorder. She smoked 10 cigarettes per day.

Visual acuity was 20/15 in both eyes. Visual fields by confrontation were normal. There was no ptosis or proptosis. She had a left face turn. Abduction was reduced to 10% in the left eye, producing 8 prism-diopters of esodeviation in primary gaze position that increased to 35 prism-diopters in left gaze. Pupils measured 6 mm in dim light and constricted briskly and equally to direct light and to near stimuli. There was no dilation lag.

Sensation in the three divisions of the fifth nerve was normal to pinprick and light touch. Corneal sensation could not be adequately assessed because of prior instillation of drops. Masseter strength was normal. Facial strength and hearing were normal, as was the rest of the neurologic examination.

MRI showed a left cavernous sinus mass and adjacent mucosal opacification in the left sphenoid sinus (Fig. 1). Although a neoplasm was considered most likely, the possibility of an inflammatory lesion involving the cavernous and sphenoid sinuses was raised. Therefore, a trial of 80 mg/day of prednisone was initiated.

One week later, the esodeviation was unchanged, and she still complained of brow pain. CT scanning showed improvement in the presumed sphenoid sinusitis, but the enhancing lesion now filled the left cavernous sinus, encasing the carotid artery and eroding through the roof of the sphenoid bone. Surgical exploration showed that the mass appeared to originate from the left trigeminal nerve.

Histopathologic evaluation of a biopsy of the tumor showed an anaplastic, spindle cell neoplasm infiltrating the trigeminal nerve and ganglion (Figs. 2 and 3). The tumor cells were immunoreactive for S-100 protein and glial fibrillary acidic protein (GFAP). Mitoses were easily found, and the tumor showed a high Ki-67 labeling...
index. Immunohistochemistry for neuron-specific enolase, chromogranin, epithelial membrane antigen (EMA), and progesterone receptors was negative. A malignant peripheral nerve sheath tumor was diagnosed. She underwent Leksell Gamma Knife stereotactic radiosurgery at a single dose of 20 Gy.

Nine months later, the patient still had occasional left brow pain. Abduction had improved to 60%, resulting in 5 prism-diopters of esodeviation in primary gaze and 20 prism-diopters in left gaze. There was now decreased corneal sensation and loss of sensitivity to light touch and sharp stimuli over the left chin. Hearing was slightly reduced on the left side. MRI showed slight shrinkage of the tumor (Fig. 1).

**DISCUSSION**

MPNSTs are rare malignancies (1–5) with a reported frequency in the general population of 0.001% (6). They arise in two principal forms, sporadic (50–70%) and in association with stigmata or a family history of neurofibromatosis type 1 (30–50%). They comprise about 6% of malignant soft tissue tumors in the body (3). About 50% occur on the trunk and about 20% in the head and neck region (1).

MPNSTs that involve the cranial nerves most often affect the trigeminal nerve (3). A mere 4.6% of MPNSTs of the trigeminal nerve occur in patients who have neurofibromatosis (1), but this figure remains weakly established (2).

Most MPNSTs arise de novo, although some arise through malignant transformation of benign schwannomas (1).
They most often present clinically with facial pain, sensory paresthesias, diminished corneal reflex, and dysfunction of muscles of mastication. Further growth causes ophthalmoplegia and lower cranial nerve involvement (2). In our patient, the facial pain was mild and overshadowed by the diplopia. Furthermore, facial sensation was spared.

Radiologically, the differential diagnosis between schwannoma and MPNST may be difficult, although extension of tumor growth along nerve roots may indicate malignancy (2). On CT, bony erosion of the basilar foramina is another sign of malignancy. Meningioma can mimic MPNST on imaging, but our patient’s age and the relative rapidity of onset of symptoms, as well as the lack of associated bone reaction near the tumor, made this an unlikely diagnosis and favored a metastatic or hematologic neoplasm or an inflammatory condition such as bacterial sinusitis, sarcoidosis, or idiopathic pachymeningitis.

Histologically, MPNSTs show plump spindle and polyhedral cells with hyperchromatic, pleomorphic nuclei, inconspicuous nucleoli, and increased mitotic figures (2,4). Immunohistochemical stains useful for diagnosis include S-100 protein, which is present in 50–70% of these tumors (1), myelin basic protein, and leucine 7. The p53 mutation is frequently expressed in these tumors, and it can serve as a marker of tumor aggressiveness. Ki-67 can be used to evaluate the growth fraction of the tumor mass (1).

There is considerable variation in the management of the MPNSTs of the trigeminal nerve. Complete resection is often not possible because of their location, and radiation therapy is given either as primary or adjuvant treatment. Chemotherapy has not been effective (2). Local recurrences have been estimated to occur in 38–45% and metastases in 40–82% of cases (1).

Our patient’s clinical features are instructive, not only because of the rarity of MPNST as the cause of her symptoms and signs but also because of the initial presentation as a sixth cranial nerve palsy with only mild facial pain and relatively normal trigeminal nerve function. Sixth cranial nerve palsy in young adults and children may be benign, but malignancy should be suspected, even if there few other signs or symptoms. Biopsy of a mass seen on neuroimaging should be performed without delay.

REFERENCES
Modified Lundie Loops Improve Apraxia of Eyelid Opening

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Graham Freeman, MSc, MCOptom, Manon Owen, MB, ChB, and Carmel Noonan, FRCOphth, FRCSI

Background: Current treatments are unsatisfactory for improving apraxia of eyelid opening, defined as a delay or inability to open closed eyelids voluntarily in the presence of intact motor pathways.

Methods: Improvement in functional health was assessed using the Blepharospasm Disability Scale (BDS) in five consecutive patients with apraxia of eyelid opening treated with wire loops affixed behind ordinary spectacles (Lundie loops) and modified to provide pressure on the brow as a stimulus to keep the eyelids elevated.

Results: All five patients showed improvement in BDS scores. The mean percentage of normal activity of the study population improved from 25% to 37.6%. Outdoor activities were not significantly altered with the use of the device.

Conclusions: Modified Lundie loops appear to be helpful in improving the functional health of patients with eyelid apraxia. These results will need to be verified in larger trials.


A praxia of eyelid opening is a nonparalytic movement disorder characterized by difficulty in voluntarily initiating the act of eyelid elevation despite preserved alertness and language comprehension (1). It is frequently seen in patients with extrapyramidal disorders such as progressive supranuclear palsy, Parkinson disease, and dystonias (2). Blepharospasm, a focal form of dystonia characterized by bilateral involuntary spasmodic eyelid closure, may lead to disability in various daily activities such as reading, watching television, walking, and household activities. In its severest form, blepharospasm results in functional blindness.

Eyelid apraxia and blepharospasm may coexist in the same patient (3).

Botulinum toxin injections and myectomy of the eyelid protractor muscles form the mainstays of treatment for blepharospasm. Treatment options for apraxia of eyelid opening are limited. Botulinum toxin injections and 1-dopa have been used with limited success (4,5). The use of sensory tricks by the patients with blepharospasm and apraxia has been reported (1,6,7). We present our experience in using a novel modification of Lundie loops, a type of ptosis prop, in the management of these patients.

METHODS

Patient Recruitment

The study was conducted in accordance with the tenets of the Declaration of Helsinki. Five consecutive patients, three women and two men, with clinically diagnosed apraxia of eyelid opening were recruited into this study. The diagnosis of apraxia of eyelid opening was made according to the criteria of Lepore and Duvoisin (2), which include 1) no sign of ongoing orbicularis oculi contraction such as lowering of the brows beneath the superior orbital margins (Charcot sign), 2) marked frontalis overaction during the period of inability to raise the eyelids, and 3) no ocular motor or ocular sympathetic nerve dysfunction or extraocular myopathy. Electromyographic studies of the orbicularis and levator muscles were not performed due to nonavailability in our setting.

On review of the case notes, one patient had progressive supranuclear palsy and one had Parkinson disease diagnosed by a neurologist. After a complete ophthalmic assessment, patients were referred to our principal optometrist for prescription of glasses with modified Lundie loops (Fig. 1).

Lundie Loops

Originally designed for patients with myasthenia gravis, the aim of Lundie loops (Fig. 1) is to provide a comfortable and unobtrusive prop for those whose eyelids tend to droop or even close completely. The prop is made in...
Lundie Loops in Eyelid Apraxia

FIG. 1. A. Glasses with Lundie loops in place. B. Loops positioned to rest on the eyebrow.

the form of a large circle of stainless steel wire that is about the same size as the spectacle lens so that the wearer looks through the middle of the prop. The upper part of the prop is fitted with a short piece of silicone tubing to give the necessary gentle grip on the skin of the eyelid. In our study, the loops were modified so that their proximal end compressed the eyebrow (Fig. 1) rather than the skin of the eyelid. The aim was to increase the proprioceptive input leading to modulation of the dystonic impulses from the basal ganglia. The prop was secured to the spectacles by drilling two small holes in the frame and pressing the ends of the wire into them.

The loops are comfortable because they are silicone-covered where they touch the skin. As fashioned by us, they exerted only very light upward pressure on the brow, and no pressure on the eye. They are safe because they have no sharp projections to injure the eyes. The design is unobtrusive when worn because the props lie within the outline of the spectacle frame.

All the patients in the study group wore prescription glasses. The loops were incorporated into their glasses. Patients were advised to continue wearing their glasses as per their normal routine. Patients were followed up at intervals of 2–3 months.

Blepharospasm Disability Scale

To evaluate the treatment outcome, we used the Blepharospasm Disability Scale (BDS) (Table 1) originally proposed by Fahn (9) for assessing the impact of blepharospasm on activities of daily living. This index is an eight-item section of the Blepharospasm Rating Scale. The instrument depends on the patient’s self-report and gives a single summary score ranging from 0 to 26 points. Higher scores indicate higher functional disability. The results are expressed as a percentage of normal activity as follows: functionally blind (0%–20% of normal activity); severely limited (21%–33% of normal activity); moderate to marked limitation (34%–57% of normal activity); minor functional limitation (58%–75% of normal activity); socially affected (76%–90% of normal activity); no limitation of activities (95% of normal activity); unaware of any difficulty (100% of normal activity). The percentage of improvement in normal activity was calculated using the formula as detailed in Lindeboom et al (8) in their study of the metric properties and clinical usefulness of the BDS in treatment outcome studies. If none of the activities is impaired and there is only impairment of patient’s social life, a sum of 90% is assigned. Those items that do not apply to a patient are eliminated from calculations; for example, a patient may have never driven or may never go to the cinema even if blepharospasm was not present.

The baseline functional state of all patients was rated with the BDS 1 month before they commenced wearing of the loops. A second interview was conducted 6–8 months after patients started the treatment, at which time the functional states of all patients were reassessed using the same scale. The duration of daily wear and the activity of maximum improvement were noted.

RESULTS

The age range of the study population was 68–83 years with a median of 72 years. Daily wear time ranged from 8 to 15 hours with an average of 11.8 hours. None of the patients reported any problems with the use of the loops. The mean preintervention BDS score was 18.8 (range 18–20) and the mean postintervention BDS score was 15.2 (range 14–16) (Table 2). Maximum improvement was reported in the categories of reading and watching television. The mean percentage scores improved from 25% (severely limited) to 37.6% (moderate limitation) (Table 3). All five patients in the study population demonstrated improvement in their BDS scores and in their percentages of normal activity. Maximum improvement was seen in the daily activities involving near and intermediate vision. None of the patients reported significant alterations in outdoor activities such as driving and walking.

DISCUSSION

Apraxia of eyelid opening occurs in 7%–10% of patients with blepharospasm (3). Whereas blepharospasm is characterized by forceful orbicularis spasms, apraxia of eyelid opening does not involve orbicularis muscle over-activity; instead, the brows are elevated due to frontalis overaction (11).
TABLE 1. Blepharospasm disability scale

<table>
<thead>
<tr>
<th>Functional Activity</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunglasses (Check one or both if they apply)</td>
<td></td>
</tr>
<tr>
<td>Need to wear sunglasses outdoors</td>
<td>Maximum points = 2</td>
</tr>
<tr>
<td>Usually wears sunglasses indoors</td>
<td>1</td>
</tr>
<tr>
<td>Driving (check one that applies)</td>
<td>Maximum points = 5</td>
</tr>
<tr>
<td>Uncomfortable, but no limitation</td>
<td>1</td>
</tr>
<tr>
<td>Cannot drive at night because of blepharospasm</td>
<td>2</td>
</tr>
<tr>
<td>Can drive in daytime, but need to prop eyelids open</td>
<td>3</td>
</tr>
<tr>
<td>Can drive only short distances</td>
<td>4</td>
</tr>
<tr>
<td>Cannot drive at all because of blepharospasm</td>
<td>5</td>
</tr>
<tr>
<td>Reading (check one if affected by blepharospasm)</td>
<td>Maximum points = 3</td>
</tr>
<tr>
<td>Uncomfortable, but no limitation</td>
<td>1</td>
</tr>
<tr>
<td>Mild to moderate limitation of viewing television</td>
<td>2</td>
</tr>
<tr>
<td>Marked limitation of viewing television</td>
<td>3</td>
</tr>
<tr>
<td>Movies (check one if affected by blepharospasm)</td>
<td>Maximum points = 3</td>
</tr>
<tr>
<td>Uncomfortable, but no limitation</td>
<td>1</td>
</tr>
<tr>
<td>Mild to moderate limitation of watching movies</td>
<td>2</td>
</tr>
<tr>
<td>Marked limitation of watching movies</td>
<td>3</td>
</tr>
<tr>
<td>Shopping (check one if affected by blepharospasm)</td>
<td>Maximum points = 3</td>
</tr>
<tr>
<td>Uncomfortable, but no limitation</td>
<td>1</td>
</tr>
<tr>
<td>Not able to shop in department store when alone</td>
<td>2</td>
</tr>
<tr>
<td>Not able to shop, even when accompanied</td>
<td>3</td>
</tr>
<tr>
<td>Walking about (check one if affected by blepharospasm)</td>
<td>Maximum points = 4</td>
</tr>
<tr>
<td>Uncomfortable, but no limitation</td>
<td>1</td>
</tr>
<tr>
<td>Difficulty walking in crowds</td>
<td>2</td>
</tr>
<tr>
<td>Not able to walk outside alone</td>
<td>3</td>
</tr>
<tr>
<td>Not able to walk indoors unassisted</td>
<td>4</td>
</tr>
<tr>
<td>Housework or outside job (check one of these)</td>
<td>Maximum points = 3</td>
</tr>
<tr>
<td>Uncomfortable, but no limitation</td>
<td>1</td>
</tr>
<tr>
<td>Difficulty working because of blepharospasm</td>
<td>2</td>
</tr>
<tr>
<td>Not able to work because of blepharospasm</td>
<td>3</td>
</tr>
</tbody>
</table>

Scale from Lindeboom et al (8).
Total maximum points = 26.

Anderson et al (3) reported that botulinum toxin injections are effective in up to 86% of patients with blepharospasm alone but only in 50% of patients with a combination of blepharospasm and eyelid apraxia. Hence, correction of the eyelid apraxia is of utmost significance in the management of patients with blepharospasm.

Botulinum toxin injections have been shown to improve lid movement metrics in patients with apraxia of eyelid opening (4). This improvement was explained by a decrease in the activity of orbicularis oculi muscle. l-Dopa has been used with some success in patients with isolated apraxia of eyelid opening (5).

Patients with eyelid apraxia use sensory tricks (gestes antagonistes) to help open their eyelid (1). Such tricks include opening the mouth, lightly touching the temporal region, putting pressure on the chin, massaging the eyelids and manually elevating the eyelids. Weiner et al (6) and Fahn (7) have reported the successful use of sensory tricks by patients with blepharospasm. There are observational case reports on the successful use of tight goggles and scleral contact lenses (12,13). These devices differ in design from the Lundie loops. The scleral contact lens has pegs on the front surface of a contact lens which help to prevent spontaneous eye closure and facilitate handling. The use of tight goggles reported by Hirayama et al (12) was based on the increased proprioceptive input from the goggles, which helped to improve apraxia.
The Lundie loops used in this study were originally designed for use by patients with myasthenia gravis associated with upper eyelid ptosis. The loops were to mechanically support upper eyelids by propping them up. We modified the loops to make them rest on the eyebrow to provide increased proprioceptive input. In keeping with previous reports (12,13), we believe the increased proprioceptive input led to modulation of the dystonic impulses from the basal ganglia and to improvement in symptoms of our patients.

The use of the BDS to study the effects of botulinum toxin in patients with blepharospasm and of eyelid opening apraxia was reported by Forget et al (4) in 2002. In another study of 32 patients with apraxia of eyelid opening, Krack et al (14) described five patients who found eyelid crutches to be useful in daily activities. The design of the crutches was not described. Our study describes the use of novel-design Lundie loops in the treatment of apraxia of eyelid opening and, for the first time, assesses the effects of treatment using the BDS.

The modified Lundie loops appear to be simple and effective in the management of patients with apraxia of eyelid opening. Our results are encouraging but will need to be verified in a much larger cohort.

Acknowledgments

We acknowledge Mr. Lundie, the original designer of the Lundic loops for his permission to use information from the original leaflet. Mr. Lundie can be reached at jlundie@remploy.co.uk.

### Table 2. Blepharospasm disability scale (BDS) scores of our study population

<table>
<thead>
<tr>
<th>Case</th>
<th>Pre-intervention BDS score</th>
<th>Post-intervention BDS score</th>
<th>Activity of Maximum Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18</td>
<td>14</td>
<td>Reading</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>16</td>
<td>Watching television</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>16</td>
<td>Watching television</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>15</td>
<td>Reading</td>
</tr>
<tr>
<td>5</td>
<td>19</td>
<td>15</td>
<td>Reading</td>
</tr>
</tbody>
</table>

### Table 4. Percentage of normal activity* in our study population

<table>
<thead>
<tr>
<th>Case</th>
<th>Pre-intervention</th>
<th>Post-intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28%</td>
<td>42%</td>
</tr>
<tr>
<td>2</td>
<td>24%</td>
<td>35%</td>
</tr>
<tr>
<td>3</td>
<td>28%</td>
<td>35%</td>
</tr>
<tr>
<td>4</td>
<td>21%</td>
<td>38%</td>
</tr>
<tr>
<td>5</td>
<td>24%</td>
<td>38%</td>
</tr>
</tbody>
</table>

Calculations were as detailed in the original article by Fahn (10). Total the points scored, divide by the maximum possible points for each specific patient, multiply the quotient by 90, and subtract from 90%.

*Formula: 90% - 90(score/maximum possible) = final score.

### REFERENCES

Vogt-Koyanagi-Harada Syndrome in a Case of Multiple Sclerosis

Javier A. Montero, MD, M. Eugenia Sanchis, PhD, and Marta Fernandez-Munoz, MD

Abstract: A 34-year-old woman in whom multiple sclerosis (MS) had been diagnosed 2 years earlier developed progressive bilateral visual loss associated with peripapillary exudative retinal detachment and other features of Vogt-Koyanagi-Harada (VKH) syndrome. She was treated with corticosteroid pulses and interferon β-1A with visual acuity improvement and resolution of the retinal detachment. This is the first reported case of VKH syndrome in a patient with MS. The combination of VKH syndrome and MS suggests a common autoimmune pathogenesis.

CASE REPORT

A 34-year-old woman was referred from the neurology clinic with progressive bilateral visual loss for the past 3 weeks. She also described decreased hearing in

FIG. 1. T2 axial MRI performed 11 months before the appearance of Vogt-Koyanagi-Harada (VKH) syndrome shows multiple hyperintense lesions in the subcortical white matter and around the corpus callosum, consistent with multiple sclerosis.
her left ear, neck stiffness, and headache during the same period. The patient had been diagnosed with MS 2 years earlier on the basis of bilateral lower limb weakness, ataxia, and optic neuritis in the right eye, as well as multiple hyperintense lesions on MRI (Fig. 1).

On our examination, visual acuity was 20/200 in the right eye and 20/160 in the left eye. Pupil constriction to bright light was reduced in both eyes, and there was a quiet anterior chamber and flat peripapillary serous retinal detachment affecting the nasal half of the macula in both eyes. The vitreous cavity was clear, and there was no retinal vascular sheathing. Optical coherence tomography (OCT) revealed neurosensory retinal detachments surrounding the optic disc and reaching the macula in both eyes (Fig. 2). Fluorescein angiography (FA) showed a pinpoint pattern of fluorescence surrounding the optic disc with leakage filling the subretinal space in the detached area and marked optic disc hyperfluorescence.

During the next 3 days, visual acuity decreased to 20/400 in both eyes as subretinal fluid leakage and retinal detachment progressed. Simultaneously, a mild painless anterior chamber reaction developed in both eyes with mutton fat keratic precipitates. A lumbar puncture revealed 63 mononuclear cells/mm$^3$. The patient was treated with 250 mg intravenous methylprednisolone three times daily for 4 days followed by 1 mg/kg oral prednisone per day. Simultaneously, interferon (IFN) $\beta$-1A was started subcutaneously three times per week (Fig. 3).

During the following 10 weeks, visual acuity slowly returned to 20/25 in the right eye and 20/15 in the left eye. The subretinal fluid disappeared, and peripapillary retinal pigment epithelial patchy atrophy was observed (Fig. 4).
The patient developed diffuse alopecia. Oral prednisone was slowly tapered and discontinued. IFN β-1A was continued for the following 6 months.

**DISCUSSION**

Common to all forms of VKH syndrome are the requirements that patients have no prior history of ocular trauma or surgery, no evidence of other ocular disease on the basis of clinical or laboratory evidence, and bilateral ocular involvement. Complete forms of VKH syndrome are characterized by diffuse choroiditis with focal areas of subretinal fluid or choroidal thickening with fluorescein angiographic abnormalities, including focal areas of delayed choroidal perfusion, multifocal pinpoint leakage, areas of placoid hyperfluorescence, pooling of subretinal fluid, and optic nerve staining. Patients with complete VKH syndrome must also have evidence of neurologic and auditory abnormalities, including meningismus, tinnitus, or cerebrospinal fluid pleocytosis, as well as integumentary signs such as alopecia, poliosis, or vitiligo (16–18). However, these integumentary signs should not occur before the onset of ocular or neurologic manifestations.

We describe an unusual patient with a combination of VKH syndrome and MS who had complete anatomic and functional recovery after systemic corticosteroid and IFN β-1A therapy. Our patient presented a complete form of VKH syndrome according to the 1978 American Uveitis Society criteria (19) revised by the International Workshop on VKH syndrome in 1999 (17). To our knowledge, this is the first case of VKH syndrome in a patient with MS to be published.

Intermediate uveitis and vasculitis of retinal vessels (5,6,20,21,22) are the typical forms of uveitis in patients with MS. Anterior uveitis may also appear, often in the form of chronic granulomatous inflammation resulting in extensive posterior synechia formation (13,14). However, our patient did not show the vascular sheathing or fluorescein leakage from posterior or peripheral retinal vessels often seen in patients with intermediate uveitis associated with MS.

Posterior uveitis has been less frequently described in association with MS, mainly as posterior granulomatous uveitis (15), symptomatic vitritis, occlusive peripheral retinal vasculitis with ischemia and neovascularization, macular edema, and epiretinal membrane formation involving the macula (10,21). In contrast, complete VKH syndrome...
includes posterior uveitis with a clear vitreous, diffuse choroiditis, diffuse or focal areas of subretinal fluid, and multifocal areas of pinpoint fluorescein leakage. Late findings in VKH syndrome may include nummular choriotinal scars and retinal pigment clumping and migration.

Although the association of VKH syndrome and MS has not been described previously, reports suggest an association with autoimmunity in the pathogenesis of both conditions (17). MS is known to be a T helper type 1 cell (Th1)-dominant condition (23), and up-regulation of Th1 cytokines has been observed in patients with VKH syndrome (24). T helper cells from patients with VKH syndrome have been found to produce predominantly Th1 cytokines, especially after stimulation in vitro (25). Miyazawa et al (26) found that concentrations of serum and CSF chemokines CXCL10/IP-10, CCL17/TARC, and CCL2/MCP-1 were essentially the same in VKH syndrome as in MS.

Our finding of VKH syndrome and MS together in one patient may draw MS closer to autoimmune diseases treated with corticosteroids and other immunosuppressive agents rather than with interferons. Currently, early and aggressive systemic corticosteroid therapy remains the standard initial treatment of VKH syndrome. In the most severe cases, intravenous methylprednisolone (up to 1 g/day) for several days can be used before beginning 1 mg/kg oral prednisolone per day (17). The duration of treatment and subsequent tapering must be individualized. Systemic therapy should not be discontinued during the 3 months after the onset of the disease because of the risk of recurrence. Systemic immunosuppressive treatment is necessary in those patients whose disease fails to respond to high-dose systemic corticosteroids or who develop intolerable adverse effects. Cyclosporine (27), tacrolimus (28), azathioprine (29), cyclophosphamide (29), and chlorambucil (30) have been used.

IFN α was initially suggested to play a role in therapy of VKH syndrome (29). Yet, episodes of VKH syndrome have been reported recently in patients with hepatitis C (31,32) and myeloma (33) who had been treated with IFN α-2b. On the other hand, a retrospective, nonrandomized study of MS patients with uveitis treated with IFN β has shown improvement in visual acuity with reductions in cystoid macular edema and vitreous and aqueous cell counts (34). In our patient, it is not clear whether the improvement was due to IFN or corticosteroid therapy. However, IFN therapy may have aided in the early tapering of systemic corticosteroid therapy.

In summary, although the pathogenesis of VKH syndrome and MS is uncertain and antigen-specific treatment strategies have not yet been developed, recent reports increasingly suggest a common autoimmune nature for both conditions (17).

REFERENCES


Mitochondrial Ophthalmoplegia With Fatigable Weakness and Elevated Acetylcholine Receptor Antibody

Raed Behbehani, FRCSC, Khaja Sharfuddin, MRCP, and J. T. Anim, FRCPath

Abstract: A 25-year-old man with chronically progressive ptosis and bilateral ophthalmoplegia displayed fatigability and fluctuation of ptosis, an abnormal single-fiber electromyogram, and a markedly elevated acetylcholine receptor antibody level. Yet a muscle biopsy showed clear evidence of a mitochondrial cytopathy, and the clinical features did not improve after treatment with prednisone. This case emphasizes the difficulty in differentiating mitochondrial cytopathy from myasthenia gravis and points out that elevated acetylcholine receptor antibody levels may occur in nonmyasthenic conditions.


Chronic progressive external ophthalmoplegia (CPEO) and ptosis are common manifestations of mitochondrial cytopathy. However, these features can also occur in myasthenia gravis, Graves disease, and brainstem lesions. Distinguishing ophthalmoplegia due to mitochondrial cytopathy from these other conditions, particularly ocular myasthenia gravis, can be difficult. We present a case of CPEO due to mitochondrial cytopathy with a diagnostically misleading combination of fatigability and an elevated acetylcholine receptor antibody level.

CASE REPORT

A 25-year-old man presented with progressive bilateral ptosis for 6 years. He denied double vision, difficulty breathing or swallowing, or other symptoms of muscle weakness. He reported that his ptosis improved with sleep and rest and with “rubbing his eyes and then blinking quickly.” He had had decreased vision in the left eye since childhood. He was otherwise in good health and using no medications. His family history was negative for myasthenia gravis.

Visual acuity was 20/30 in the right eye and 20/400 in the left eye. He recognized all of the pseudoisochromatic color plates with the right eye but none with the left eye. The pupils were of normal size and equally reactive to light with no relative afferent defect. Intraocular pressures were 12 mm Hg in both eyes. Bilateral ptosis was present, which was fatigable on sustained up gaze (Fig. 1A). The degree of ptosis varied during the examination; blinking reduced it for 1–2 minutes (Fig. 1B). There was moderate orbicularis oculi weakness on attempted forced eyelid closure bilaterally. Ocular ductions were reduced in all gaze directions (Fig. 2). He had a comitant left exotropia of 10 prism-diopters (PD) and right hypertropia of 16 PD in upgaze and 14 PD in downgaze. Dilated fundus examination was normal. Automated perimetry was normal in the right eye and showed a central scotoma in the left eye.

MRI of the brain and orbit was normal. The acetylcholine receptor antibody level was markedly elevated at 16.7 nmol/L (normal <0.2 nmol/L). Repetitive nerve stimulation electromyography (EMG) was normal. However, single-fiber EMG of the orbicularis oculi showed a mean value of consecutive differences (MCD) of 53.1 μs, 3/22 blocks, and 12/22 abnormal end plates. These findings were interpreted as indicating a neuromuscular transmission defect. CT scanning of the upper mediastinum did not identify any thymic masses. Needle EMG of the deltoid and the orbicularis oris muscles showed some polyphasic potentials, considered a myopathic pattern. A electroretinogram (ERG) showed low amplitude photopic and scotopic responses and a diminished response to a 30 Hz flicker in both eyes.

The patient was treated with 60 mg pyridostigmine three times per day and 10 mg prednisone every other day for 2 weeks, which was then increased to 40 mg daily for 4 weeks. This treatment did not lead to objective improvement in either the ptosis or ocular motility abnormality.
Electron microscopical examination of a deltoid muscle biopsy showed widespread subsarcolemmal and sarcoplasmic deposition of lipid droplets and vacuolar degeneration in some muscle spindles. These changes were interpreted as indicating a myopathy with dystrophic features. Histopathologic and electron microscopical examination of an orbicularis oculi specimen showed focal myofibrillar degeneration with associated loss of the Z-discs and I-bands. The main abnormality was in the mitochondria, which showed subsarcolemmal and sarcoplasmic aggregation in large numbers. There was variation in the size and shape of the mitochondria with distortion of cristae, the latter assuming a “fingerprint” pattern in many areas. These findings were interpreted as being consistent with a mitochondria cytopathy (Fig. 3).

The patient was followed for 2 weeks after the surgery. Eventually he discontinued all medications as they appeared to be ineffective. He was then lost to follow-up.

**DISCUSSION**

We present a diagnostically confusing case of ophthalmoplegia and ptosis due to mitochondrial cytopathy with concurrent features of myasthenia, namely fatigable and fluctuating ptosis and high acetylcholine receptor antibody levels. There were many features suggestive of mitochondrial cytopathy, such as a long-standing course of ptosis, initial absence of diplopia, cone-rod dysfunction, and a lack of response to corticosteroid treatment. Although our patient’s ERG was consistent with cone-rod dysfunction, he did not have the pigmentary retinal findings seen in

![FIG. 1. A. Marked bilateral ptosis is present. B. With blinking, ptosis briefly improves.](image1)

![FIG. 2. Ductional deficits are present in all gaze directions in both eyes.](image2)
Mitochondrial Ophthalmoplegia

Kearns-Sayre syndrome. The degree of retinal dysfunction was unusually asymmetric but supportive of the diagnosis of mitochondrial cytopathy. He eventually developed diplopia and exotropia, but this has been reported in mitochondrial cytopathy (1).

In our patient, the abnormal single-fiber EMG further suggested a diagnosis of myasthenia gravis. However, it should be emphasized that although single-fiber EMG is a very sensitive test for myasthenia gravis, it is not specific for that condition (2,3). Increased jitter and/or blocking have been reported in mitochondrial cytopathy (4,5). It has been postulated that a primary defect in neuromuscular transmission may be present in mitochondrial cytopathy (4).

Perhaps the most diagnostically confusing feature of our patient is the presence of a markedly elevated acetylcholine receptor antibody level. It is unclear whether this elevation represents an epiphenomenon or whether he has mitochondrial cytopathy and myasthenia gravis. A trial of pyridostigmine and corticosteroids did not produce any significant therapeutic effect. Suzuki et al (6) reported a 59-year-old patient with mitochondrial diabetes, facial palsy, ophthalmoplegia, and hearing loss in association with mildly elevated acetylcholine receptor antibodies. The patient had negative results for repetitive nerve stimulation and a negative edrophonium chloride (Tensilon) test. The acetylcholine receptor antibody level in this patient was only marginally elevated at 0.6 nmol/L (normal is <0.2 nmol/L). Mitsikostas et al (7) reported an elevated acetylcholine receptor antibody titer in two elderly women with external ophthalmoplegia, elevated lactate acid, and ragged red fibers. Elevated acetylcholine receptor antibody levels can also be detected in autoimmune conditions such as primary biliary cirrhosis, Eaton Lambert syndrome, and Graves ophthalmopathy (8-12). Jacobson et al (8) found that 4 of 50 (8%) consecutive patients with Graves ophthalmopathy had elevated acetylcholine receptor antibodies. No obvious differences existed between the seropositive and seronegative groups. None of the four seropositive patients developed signs of myasthenia gravis during the median follow-up period of 4.5 years. It is possible in our patient that the very high acetylcholine receptor antibody level is caused by mitochondrial damage in the skeletal muscles triggered by an autoimmune response to the acetylcholine receptor, or that he has an autoimmune condition that we did not recognize.

REFERENCES

Accelerated Growth of an Orbital Schwannoma During Pregnancy

Nobuo Sugo, MD, Kyousuke Yokota, MD, Masaaki Nemoto, MD, Tsutomu Hatori, MD, Toshiyuki Kano, MD, Syozo Goto, MD, and Yoshikatsu Seiki, MD

FIG. 1. Three months before pregnancy, T2 axial MRI (top left) shows a right intraconal mass of mixed signal intensity that partially enhances on postcontrast T1 axial MRI (top right). Immediately after delivery, T2 axial MRI (bottom left) shows a marked increase in the cystic mass with slight enhancement of its wall on T1 axial MRI (bottom right).

Abstract: An incidentally diagnosed unilateral orbital mass in a 34-year-old woman grew at an accelerated rate during pregnancy with deterioration of visual function. Removed early after delivery by a transcranial approach, the tumor was histologically diagnosed as a richly vascularized cystic schwannoma containing red blood cell components. The accelerated tumor growth was attributed to intratumoral hemorrhage. Although acoustic schwannomas have been reported to enlarge during pregnancy, this phenomenon has only been described once for orbital schwannomas. Because this type of tumor may enlarge during pregnancy and threaten visual function, surgery should not be delayed.

(J Neuro-Ophthalmol 2007;27:45-47)

A 34-year-old woman with head trauma underwent brain CT that incidentally showed a right orbital mass. There were no skin findings suggestive of neurofibromatosis. The 24 × 14 × 13 mm mass showed high signal intensity at the periphery and irregular mixed intensity signal in the center on T2 MRI; it was hypointense on T1 MRI and displayed partial enhancement (Fig. 1).
Cerebral angiography revealed no abnormalities in the arterial or venous phase. The patient had normal visual acuity and a normal visual field. She had only mild exophthalmos with intact extraocular movements. After discussing the problem with the patient, we decided not to operate on the tumor. Five months after the first examination, she was found to be 9 weeks pregnant. At 32 weeks of pregnancy, the right exophthalmos became rapidly aggravated (20 mm on the right and 14 mm on the left), and right abduction was reduced to 70%. Visual acuity and visual field remained normal. Intraocular pressures were 16 mm Hg in the right eye and 16 mm Hg in the left eye.

Within days of a normal delivery at 37 weeks of gestation, MRI showed marked interval growth of the tumor to $34 \times 27 \times 29$ mm; the fluid in the cystic mass had markedly increased (Fig. 1). Nearly complete right ophthalmoplegia subsequently developed. Intraocular pressures were 25 mm Hg in the right eye and 16 mm Hg in the left eye. Visual acuity had deteriorated to 20/200 in the right eye. Right visual field examination disclosed a central scotoma.

To preserve visual function, the orbital cystic lesion was removed by a microsurgical transcranial approach on the 15th day after delivery. Orbital unroofing by a frontotemporal approach revealed a tumor mainly in the intraconal space. The fluid obtained by puncturing the cystic mass was yellowish and serous and contained red blood cell components. Because the tumor was firmly adherent to the optic nerve, it was resected subtotally. It was difficult to identify the nerve from which the tumor arose.

The histologic diagnosis was schwannoma with Antoni A and B features (Fig. 2A). The tumor was richly vascularized and displayed scattered aggregates of vessels (Fig. 2B). Immunohistochemical studies showed that the tumor was positive for S-100, negative for epithelial membrane antigen, and negative for progesterone and estrogen receptors.

The patient had an uneventful postoperative course with improvement of the exophthalmos and preservation of visual function. Intraocular pressures were 16 mm Hg in the right eye and 16 mm Hg in the left eye. Visual acuity had improved to 20/30 bilaterally. The central scotoma was markedly reduced. After surgery, she developed a mild right abduction deficit. The postoperative ptosis disappeared 2 months later.

Among all orbital tumors, orbital schwannomas are relatively rare (1-3). There has been only one reported case of an orbital schwannoma with rapid growth during pregnancy (4). On the other hand, there have been many reports of acoustic schwannomas enlarging during pregnancy, resulting in the appearance and aggravation of symptoms (5-8). Whether pregnancy-related hormonal changes are directly involved in the mechanism of schwannoma growth acceleration is controversial (4,9). Chang et al (4) suggested progesterone receptors as a mechanism of the rapid growth of the orbital schwannoma in their patient. Immunohistochemical studies in our patient showed that the tumor was negative for progesterone and estrogen receptors, which suggests that another factor, such as intratumoral hemorrhage, accounted for the growth of the tumor. The increased vascularity of these tumors makes them more vulnerable to intratumoral hemorrhage (7). In this patient, serial MRI showed increased cystic fluid accumulation, and the cystic fluid obtained during surgery contained red blood cell components. In addition, pathologic examination showed that the wall of the tumor was richly vascularized. These findings suggest that repeated intratumoral hemorrhage resulted in tumor growth. Because orbital schwannomas developing during pregnancy threaten visual function by rapid growth, surgery should not be delayed.

**REFERENCES**

Transorbital Intracranial Penetrating Injury From Impaling on an Earpick

Taro Yamashita, MD, Takeshi Mikami, MD, Takeo Baba, MD, Yoshihiro Minamida, MD, Toshiya Sugino, MD, Izumi Koyanagi, MD, Tadashi Nonaka, MD, and Kiyohiro Houkin, MD

FIG. 1. A. The earpick penetrates the left orbit above the eye. B. CT reconstruction shows the trajectory of the earpick (arrow). C. Three-dimensional CT shows the earpick (white arrow) reaching into the prepontine cistern via the superior orbital fissure (black arrowhead). The earpick is adjacent to the left internal carotid artery (black arrow). D. Intraoperative photograph shows the top of the earpick (black arrow) lying between the fifth cranial nerve (black arrowhead) and the sixth cranial nerve. The superior petrosal vein (white arrow) and seventh cranial nerve (white arrowhead) are shown.

Abstract: An inebriated 86-year-old man impaled himself on a wooden earpick that penetrated through the superior orbital fissure into the prepontine cistern. The patient underwent surgery immediately by a lateral suboccipital approach, and the earpick was pulled out through the wound with control of hemorrhage from the cavernous sinus. He survived this event with no neurologic deficits apart from complete ipsilateral ophthalmoplegia and ptosis. Prompt imaging and surgical intervention allowing direct visualization of the foreign body and prevention of intracranial complications are part of proper management of this problem.

(J Neuro-Ophthalmol 2007;27:48-49)

An 86-year-old intoxicated man stood up, lost his balance, and fell down on a pen stand. The wooden earpick in the pen stand penetrated his left upper lid. On
admission the patient was alert and oriented. The earpick had entered the left orbit just above the eye (Fig. 1A). Visual acuity was normal in both eyes, but there was complete left ophthalmoplegia and ptosis. The pupillary diameters were 3 mm in the right eye with normal constriction to light and 6 mm in the left eye with no constriction to light.

Three-dimensional CT scans documented the trajectory of the earpick (Fig. 1B). It had penetrated through the left superior orbital fissure, passed into the cavernous sinus just lateral to the left internal carotid artery, and protruded into the prepontine cistern (Fig. 1C). The brainstem did not appear to be deviated or contused. The patient immediately underwent surgery under general anesthesia. The top of the earpick was visualized microscopically via a lateral subtemporal approach. The earpick lay between the left fifth and sixth cranial nerves (Fig. 1D). There was a little hematoma around the earpick but no active bleeding. The earpick was pulled gradually in the direction from which it had entered, at which point venous bleeding was observed from the cavernous sinus. However, hemostasis was easily achieved with oxidized cellulose sheets.

The patient was alert just after the surgery, and his postoperative course was uneventful. He was discharged 1 month after the surgery with complete left ophthalmoplegia and ptosis but intact visual function. At the last follow-up examination 6 months after the injury, the deficits were unchanged, and visual function remained normal.

Ocular or orbital injury in civilian life is rare. Most cases have been caused by pens, knives, or chopsticks (1–4). Ophthalmologists and neurosurgeons have to consider the possibility of intracranial penetration and its path. There are three possible paths for penetration of the cranium through the orbit: through the orbital roof (3,5), the superior orbital fissure (6,7), and the optic canal (1). The most frequent path is through the orbital roof, and this often leads to frontal lobe contusion (3,5). The second most frequent path is through the superior orbital fissure, which occasionally results in the penetrating object’s reaching the brainstem through the cavernous sinus (6,7). Our case demonstrated this latter pattern. Fortunately the top of the earpick reached only the prepontine cistern and did not injure the brainstem.

The intracranial complications of transorbital penetrating injury include ventricular damage, brainstem injury, vascular injury, carotid-cavernous sinus fistula, pneumocephalus, subdural hemorrhage, subarachnoid hemorrhage, and intracerebral hemorrhage (8–10). Thin-slice CT and its reconstruction are necessary to simultaneously evaluate the trajectory and possible complications of these penetrations. Wooden foreign bodies may sometimes be problematic for imaging diagnosis because intracranial wood may show various degrees of attenuation on CT (1). In our patient, the dry wood earpick displayed low attenuation.

The favored strategy for the treatment of penetrating injury is early surgical exploration (2,3,5). Early radical debridement and removal of the retained fragment are mandatory to prevent potentially fatal infectious complications (11). A wooden foreign body is especially infectious because the porous organic material provides good culture conditions for bacterial agents (12). Thin-slice CT and MRI facilitate surgical exploration.

REFERENCES
Papilledema in Obstructive Hydrocephalus Caused by Giant Cell Astrocytoma of Tuberous Sclerosis

Deborah Y. Chong, MD, Parima Hirunwiwatkul, MD, Paul E. McKeever, MD, PhD, and Jonathan D. Trobe, MD

Abstract: A 5-year-old girl with progressive hemiparesis and headache was found by brain imaging to have a large tumor centered at the foramen of Monro, blocking cerebrospinal outflow and producing massive lateral ventriculomegaly. Total excision of the mass led to a pathologic diagnosis of giant cell astrocytoma. Dermatologic abnormalities had been detected shortly after birth but were unexplained. Abdominal imaging disclosed renal cysts, and ophthalmologic examination disclosed papilledema and retinal plaques. On this basis, a diagnosis of tuberous sclerosis (TS) was finally made. Two months after surgery, papilledema had resolved, and visual function appeared to be normal. Although the patient apparently escaped visual loss, other reports affirm that giant cell astrocytoma, a common tumor in TS, may go undetected for long enough to produce irreversible optic neuropathy from chronic papilledema. Because patients with TS may not report visual loss, they should undergo periodic ophthalmologic screening.

(J Neuro-Ophthalmol 2007;27:50-54)

A 5-year-old girl presented with a 2 month history of progressive right hemiparesis, behavioral changes, morning headaches, and emesis. Brain MRI revealed a large intraventricular mass centered within the foramen of Monro and left lateral ventricle and extending into the right lateral ventricle (Fig. 1). The lateral ventricles were abnormally dilated.
Papilledema in Giant Cell Astrocytoma


FIG. 2. Hypopigmented macule on right upper forehead representing an ash-leaf spot (arrows) and erythematous papules over nasal bridge and malar eminences consistent with angiofibromas (arrowhead).

There was no history of developmental delay or seizures. Her parents and a dermatologist had noted hypopigmented macules 5 days after birth and erythematous papules over the midface at age 3 (Fig. 2), but no diagnosis was made. The combination of skin lesions and the brain mass, which appeared radiologically to be a subependymal giant cell astrocytoma, suggested a diagnosis of tuberous sclerosis (TS).

FIG. 3. Abdominal postcontrast T1 axial MRI demonstrates cysts in the left kidney (arrows).

The patient underwent an abdominal MRI that showed renal cysts (Fig. 3) and a cardiac nuclear perfusion study that demonstrated a left ventricular aneurysm.

The large intraventricular brain mass was resected, and pathologic evaluation confirmed the diagnosis of giant cell astrocytoma (Fig. 4). The tumor was composed mainly of large plump astrocytic cells that were usually uninucleated. Multinucleated cells with two or three nuclei were uncommon. Although the nuclei were pleomorphic, a clue to their relatively benign nature included rounded borders without sharp indentation of the nuclear membranes (Fig. 4A). Mitotic activity was minimal. The MIB-1 proliferation index varied from zero to a maximum of 13%.

FIG. 4. Pathology of excised intraventricular giant cell astrocytoma.
A. Pleomorphic cells with large, rounded nuclei that are either centric or eccentric within abundant finely granular cytoplasm. Giant cells greater than 50 μm in diameter mingle with smaller cells. Many extend long cellular processes. Their nuclei have rounded borders (arrow) without sharp indentations of their nuclear membranes. Small vessels have thin walls (arrowhead). Hematoxylin and eosin (H&E) stain. B. Neoplastic astrocytes stain positively for glial fibrillary acidic protein (GFAP). GFAP-positive cellular processes extend from these cells (arrow). The thin walls and contents of vessels do not express GFAP (arrowhead). C. Large “kissing neurons” (arrow) stain positively for neurofilament protein (NFP). D. A distinct border of the tumor lies just below the ependymal lining (arrow) of the lateral ventricle. These tumors often demonstrate biphasic regions that have cellular (c) and microcystic fibrillar (f) zones. H&E stain.
Eleven days after surgery, ophthalmologic examination disclosed normal visual acuity, confrontation visual fields, ocular motility, pupillary reflexes, intraocular pressures, ocular adnexae, and anterior segments. Ophthalmoscopy revealed bilateral optic disc swelling (Fig. 5A) and translucent, noncalcified lesions in the retinal nerve fiber layer in the right eye (Fig. 5C). Within 2 months after tumor resection, the papilledema had resolved (Fig. 5B).

By 4 months after surgery, all neurologic symptoms had resolved. MRI revealed that the tumor had been among different microscopic fields. Few nuclei overexpressed p53. Most of the neoplastic cells expressed glial fibrillary acidic protein (GFAP) (Fig. 4B). The pattern of GFAP expression was astrocytic, with GFAP extending out into long, stellate cellular processes. A few cells expressed neurofilament protein (Fig. 4C). This expression is more common in giant cell astrocytomas than in astrocytomas of higher grade and has generated debate about classification and nomenclature of this tumor (1–3). The tumor margin within brain tissue was distinct (Fig. 4D).
FIG. 6. Postoperative MRIs. Axial FLAIR (A), postcontrast T1 coronal (B), and postcontrast T1 sagittal (C) MRIs show complete resection of the tumor and decompression of the lateral ventricles. Persistent subcortical nodules (arrowheads) and a subependymal nodule (arrow) are visible.

completely resected, and the ventricles were decompressed (Fig. 6).

This case is presented to highlight the threat to vision from chronic papilledema caused by obstructive hydrocephalus induced by blockage of the foramen of Monro from a subependymal giant cell astrocytoma in TS. Our patient maintained full visual function, presumably because the papilledema was not severe. Other patients may not be so fortunate (2,4,5).

Occurring in approximately 6%-19% of patients with TS, giant cell astrocytomas are considered histologically benign but may grow silently to an enormous size, as exemplified by our patient. Growth may proceed for a long time without causing headache or other neurologic symptoms. The visual loss from undetected chronic papilledema may go unnoticed until it encroaches on the fixational area. Even then, patients with TS may not report it because of mental incapacity. Visual loss has been reported in 14%-67% of patients with TS who have subependymal giant cell astrocytomas (1–3). Despite surgical decompression, optic nerve damage can persist or even progress (2,4,5). Our patient had dermatologic signs of TS noted shortly after birth and at age 3 but did not undergo neuroimaging to evaluate for an intracranial mass until she presented at age 5 with neurologic symptoms. She did not have an ophthalmologic examination until after hydrocephalus was noted on neuroimaging and the tumor had been resected.

Subependymal giant cell astrocytomas may cause not only visual loss but also death. They are blamed for 25% of deaths in TS, with 12.5% directly resulting from elevated intracranial pressure (6). Poorer outcomes have been noted in patients older than 11 or 12 years at the time of resection of the tumor (2,5).

Because ophthalmoscopy is difficult for non-ophthalmologists, it is reasonable for all patients with TS to undergo periodic ophthalmologic examinations to rule out papilledema. The finding of papilledema would mandate neuroimaging. Because giant cell astrocytomas can recur after surgical resection and evolve from smaller subependymal nodules (1), periodic follow-up ophthalmoscopy is also reasonable.

Visual loss also occurs rarely in the setting of retinal astrocytic hamartomas. Although these are typically static or slow-growing lesions (7), they may give rise to vitreous hemorrhage (8), exudative retinal detachment (9), neovascular glaucoma (9), and invasive perforation of the sclera (9). In consideration of these facts, ophthalmologic monitoring is warranted.

Lastly, consultation with specialists in other fields may also assist in the diagnosis and management of TS. Dermatologic examination for ash-leaf spots (hypopigmented macules), shagreen patches (leathery connective tissue nevi), facial angiofibromas (erythematous papules formerly termed “adenoma sebaceum”), fibrous plaques of the forehead (raised, discolored patches), and periungual fibromas (fleshy tumors around or underneath the nail) may contribute to making an initial diagnosis of TS (10). Patients should also undergo evaluation for renal cysts and angiomylipomas. Although rare, renal failure, significant hemorrhaging, and malignant transformation can occur from these renal lesions (10). Furthermore, patients should
be screened for cardiac rhabdomyomas, which can cause cardiac arrhythmias and congestive heart failure, and pulmonary lymphangiomyomatosis, which can lead to dyspnea and pneumothorax (10).

REFERENCES

Susac Syndrome in a Patient With Hepatitis C

Anand Chawla, MBChB, Sivakumar Sathasivam, MBChB, MRCP, Rakhee Nayar, MBChB, and Mark Doran, MBChB, FRCP

Abstract: A 38-year-old woman seropositive for hepatitis C developed headache, sensorineural hearing loss, encephalopathy, and retinal arteriolar occlusions. Brain MRI showed signal abnormalities in the basal ganglia and corpus callosum. These features are consistent with Susac syndrome, a multifocal central nervous system disorder of uncertain etiology. This is the first reported case of Susac syndrome in a patient with hepatitis C.

(A) 38-year-old woman presented with a 3 week history of worsening frontal headaches. The headache was worse in the morning and improved throughout the day. There were no precipitating factors and she had never had similar episodes of headache. A few days later she developed bilateral deafness that progressed over 2 weeks.

The patient noticed that her speech had become slurred. She also gave a history of having memory loss over the preceding 2 weeks. Furthermore, she also reported mood disturbance, fluctuating confusion, agitation, and a feeling of unsteadiness while walking. She had no visual symptoms.

She had suffered from eczema and anxiety and was an intravenous drug abuser. She was taking regular medications and had no allergies. She smoked 20 cigarettes per day and reported minimal alcohol intake recently, although she had previously been an alcoholic. She lived with a male partner and her 5-year-old child.
A general physical examination was unremarkable. However, on neurologic examination, she was vague, confused, and dysarthric. Her Mini-Mental State Examination score was 14/30. She was disoriented to time, place, and person and had impaired delayed recall. Visual acuity was normal at 20/20 in both eyes. She had obvious deafness, but because of her confusion, it was not possible to do formal testing to determine whether the hearing loss was conductive or sensorineural. Speech was slurred. Limb coordination was normal, but gait was unsteady. The remaining neurologic examination was normal.

Hematologic and biochemical profiles were normal. Autoantibody, VDRL, and human immunodeficiency virus (HIV) tests were also negative. Antistreptococcal antibody titers were minimally elevated, and cytomegalovirus IgG was elevated. She was hepatitis C–positive with a high viral load and a high level of replication. The liver profile was normal.

An electroencephalogram showed generalized slowing of background rhythm to the delta/theta range. Brain MRI showed high signal abnormalities on FLAIR and T2 sequences in the cerebral white matter involving the corpus callosum and basal ganglia (Fig. 1). A lumbar puncture was normal except for a protein level of 81 mg/dL.

Ophthalmologic consultation later yielded the finding of multiple bilateral retinal arteriolar occlusions (Fig. 1). An audiogram demonstrated mild bilateral sensorineural hearing loss.

Therapy was initiated with 75 mg aspirin once daily and a 3 day course of 1 g intravenous methylprednisolone daily. She showed only moderate improvement and was therefore given a 5 day course of intravenous immunoglobulin, but still showed little immediate improvement. She is taking 75 mg aspirin daily on a long-term basis.

After 1 month, the gait disturbance had resolved, hearing had improved, and confusion had lessened, but a formal psychometric assessment demonstrated that her IQ remained subnormal relative to an expected level.

After 2 months, she still had a mild cognitive deficit, and her hearing was still improving. She still had evidence of retinal arteriolar occlusions, but no new lesions had developed.

In 1979, Susac, Hardman, and colleagues (1) described two young women who presented with a triad of encephalopathy, retinopathy (arteriolar occlusions), and hearing loss. Subsequent brain biopsy showed multifocal microinfarction, and the authors suggested that the condition represented a microangiopathy of the brain, retina, and cochlea. The condition is thought to mainly affect women between the ages of 18 and 40 years (2-4). The diagnosis was made by the recognition of the clinical and MRI findings (1-7). In other cases, brain biopsy is needed for diagnostic confirmation; the biopsy should show microangiopathic infarcts without evidence of vasculitis. The hearing loss and visual disturbance are often asymmetrical, as in our patient, and there have also been reports of patients in whom not all components of the clinical triad are found (2,3).

Approximately 70 cases of Susac syndrome have been reported (1-11). The connection to viral disease is not well developed. Nicolle and McLachlan (8) described a 24-year-old woman who had prodromal symptoms of fever, cough, and coryza before developing the symptoms of Susac syndrome. Coppeto et al (9) described a patient who had developed a sore throat and photophobia before developing the syndrome. Altogether, there have been six reports in which a viral illness has been thought to precipitate this syndrome, although no viral agent has been identified (10). Our case is the first report of Susac syndrome in a patient seropositive for hepatitis C. The relevance of this finding to the neurologic manifestations is unclear, but the absence of any known etiologic factor, together with the previous reports suggesting a viral link to this syndrome, invites the consideration that it may play a causative role.

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Rethinking Neuromyelitis Optica (Devic Disease)

Shelley Ann Cross, MD

Abstract: Neuromyelitis optica (NMO), or Devic disease, has been distinguished from multiple sclerosis (MS) by the presence of optic neuritis that is usually bilateral, simultaneous, and often severe, myelopathic findings accompanied by longitudinally extensive spinal cord imaging abnormalities, no brain imaging abnormalities typical of MS, and often rapid progression to debility and even death. Researchers at the Mayo Clinic have identified an immunoglobulin marker of NMO (the “NMO antibody”) that binds selectively to the aquaporin-4 water channel and may play a causative role. This marker has been found in Japanese patients with opticospinal MS, prompting the suggestion that NMO and Japanese opticospinal MS are the same disorder. The NMO antibody, which predicts frequent relapse of myelopathy and optic neuritis, is also found in patients with lupus erythematosus and Sjogren syndrome who also have severe optic neuritis and longitudinally extensive myelitis. Because this antibody is also found in patients with optic neuritis and myelitis who have brain signal abnormalities atypical of MS, the diagnosis of NMO has been revised to allow inclusion of these brain imaging abnormalities. Proper distinction of NMO from MS is important because the two disorders may respond differently to immune modulatory therapy.

The distinction between neuromyelitis optica (NMO), or Devic disease, and multiple sclerosis (MS) has long been unclear. Traditionally, NMO is believed to differ from MS by causing very severe, often bilateral, optic neuritis and longitudinally extensive MRI spinal cord lesions but no MRI brain lesions and aggressive progression to debility and death. In the past 7 years, investigators at the Mayo Clinic have made an effort to delineate objective criteria to distinguish NMO from MS. Their efforts have resulted in a proposed redefinition of the diagnostic criteria.

THE THREE PHENOTYPIC FORMS OF NEUROMYELITIS OPTICA

The NMO phenotype occurs in three contexts:

1. MS. The optic nerves and spinal cord are the principal or only targets. MRI studies show scattered and also periventricular brain lesions and patchy and peripheral rather than central and longitudinally extensive spinal cord lesions. Oligoclonal bands are present in the cerebrospinal fluid (CSF). The pathology consists of demyelination but generally not necrosis.

2. True NMO. Patients have recurrent severe optic neuritis and myelitis with longitudinally extensive MRI spinal cord lesions. There are no CSF oligoclonal bands. The pathology shows necrosis. Japanese and African-American patients with “opticospinal MS” may belong in this group (1,2).

3. Other autoimmune diseases. Optic neuritis and myelitis are found in systemic lupus erythematosus (SLE), Sjogren syndrome (SS), sarcoidosis, vasculitis, Behcet disease, tuberculosis, and paraneoplastic disorders (1).

WHY IS THE DISTINCTION BETWEEN NEUROMYELITIS OPTICA AND MULTIPLE SCLEROSIS IMPORTANT?

The importance of separating NMO from MS is twofold. 1) NMO has a worse outcome than MS, with frequent and early relapses. Within 5 years of onset, 50% of patients are blind in both eyes and cannot walk unassisted, and 20% die of respiratory failure due to cervical myelitis (3). 2) NMO responds to immunosuppressive therapy with agents such as azathioprine and rituximab (4) and to plasmapheresis, whereas the currently promoted treatment of MS includes immune-modulating agents such as interferon β.

THE NEUROMYELITIS OPTICA ANTIBODY

Beginning in 2003, Mayo Clinic investigators began publishing articles on NMO that described a serum autoantibody marker and redefined the clinical criteria for NMO diagnosis. In 2004, Lennon et al (5,6) identified an IgG marker of NMO that is purported to allow distinction from MS.
The investigators prospectively tested serum samples from 124 patients with clinical NMO or high risk for NMO. In the first subgroup were 102 North American patients. Of these, 45 had definite NMO, or remained at high risk for NMO and 22 were found to have “classic” MS. NMO was defined as optic neuritis, acute myelitis, and no imaging evidence of demyelinating disease except in the optic nerves and spinal cord. Supportive evidence included either one major criterion or two minor criteria. The major criteria were 1) normal brain MRI at outset, 2) a spinal cord MRI signal abnormality extending three or more vertebral segments, and 3) CSF pleocytosis \( > 50 \times 10^{-6} \) white blood cells/L, or \( > 5 \times 10^{-6} \) neutrophils/L. The minor criteria were 1) bilateral optic neuritis, 2) severe optic neuritis with irreversible visual acuity loss worse than 20/200 in at least one eye, and 3) severe weakness in at least one limb.

In the second subgroup were 22 Japanese patients: 11 with definite opticospinal MS, 1 considered to be at high risk of opticospinal MS, 5 with classic MS, and 5 with cerebral infarction. The criteria for the diagnosis of opticospinal MS were exactly those used to diagnose NMO.

In addition to the 124 patients with NMO or high risk of NMO, there was a control group of 75 patients with classic MS (19 patients), myasthenia gravis (10 patients), paraneoplastic visual loss with or without optic neuritis (16 patients) Sjögren syndrome (12 patients), vasculitis with neurological complications (9 patients), and other disorders (9 patients) including paraneoplastic myelopathy with CRMP-5, vitamin B12 deficiency, sarcoidosis, lymphoma, glioma, normal pressure hydrocephalus, and conversion reaction.

In addition, further patients were ascertained retrospectively by virtue of incidental detection of an antibody which turned out to be the NMO IgG. These were patients with multifocal neurologic disease suspected of having a paraneoplastic syndrome.

Using indirect immunofluorescence on a substrate of mouse central nervous system (CNS) tissue, the Mayo researchers identified, in the sera of patients with NMO and Japanese opticospinal MS, a distinctive IgG staining pattern localizing to the blood-brain barrier and partly colocalizing with laminin. Seropositivity was present in 60 (75%) patients with NMO, 7 (58%) Japanese patients with opticospinal MS, and 1 (10%) of 10 non-Japanese patients with classic MS, but in none of the North American patients with classic MS, non-MS autoimmune diseases, or other control diseases. Further testing of patients with varying NMO disease burden and activity will be needed to determine the exact incidence and conditions of positivity.

THE NEUROMYELITIS OPTICA ANTIBODY AND THE AQUAPORIN-4 WATER CHANNEL

The NMO IgG autoantibody was subsequently shown to bind selectively to the aquaporin-4 (AQP4) water channel (7), a component of the dystroglycan protein complex located in astrocytic foot processes at the blood-brain barrier. Because of the location of the antigen, it is speculated that this NMO IgG is not merely a marker but a causative agent, as is the case, for example, with the muscle acetylcholine receptor antibodies of myasthenia gravis and the P/Q-type calcium channel antibodies associated with Lambert-Eaton syndrome. AQP4 is the first water channel-specific autoantibody to be identified.

Aquaporin is the predominant water channel in the CNS. Areas of particularly high concentration of this protein are the spinal cord, the optic nerves, the hypothalamus, and the periventricular regions (8). The localization of AQP4 in the spinal cord is consistent with the immunopathology of NMO, which affects both gray and white matter, and for unknown reasons is largely restricted to the spinal cord and optic nerves (11). IgG, IgM, and products of complement activation are deposited in a perivascular pattern in NMO, suggesting a pathogenic role for the autoantibody (9). Blood vessels within demyelinating lesions are thickened and hyalinized. Active lesions exhibit tissue swelling, infiltrating polymorphonuclear macrophages, activated microglia, demyelination, axonal loss, prominent necrosis, and variable degrees of perivascular inflammation with prominence of cosinophils and products of their exocytosis. Chronic lesions show gliosis, cystic degeneration, cavitation, and atrophy. These findings are consistent with a humoral effector mechanism in NMO that is initiated by binding of the NMO autoantibody at the blood-brain barrier (9).

Pathologically, NMO shares with MS a pattern of focal demyelination, inflammation, scar formation, and axonal destruction but differs in having an intense perivascular response, prominent necrosis, and cavitation (9).

PREDICTIVE VALUE OF THE NEUROMYELITIS OPTICA ANTIBODY

The presence of the NMO IgG autoantibody in the serum of a patient with an initial attack of longitudinally extensive transverse myelitis predicts a myelopathic or optic neuritis relapse within 12 months with more than 50% certainty (10). Weisshenker et al (10) evaluated 29 patients with a first attack of transverse myelitis with an MRI lesion spanning three or more vertebral segments. Of 23 patients followed for 1 year, 9 were seropositive for the NMO IgG autoantibody. Within 1 year, 5 of 9 patients had a second event involving recurrent transverse myelitis in 4 patients and optic neuritis in 1 patient. After 1–7 years of follow-up, none of the 14 patients who were seronegative for the NMO IgG autoantibody had a relapse of myelitis or optic neuritis. In 80 patients with NMO, Wingerchuk et al (11) found that mortality due to relapsing NMO was related to a higher attack frequency during the first 2 years of disease and...
worse motor recovery after the initial myelitis event. These features may facilitate design of treatment trials.

Wingerchuk et al (12) also studied 96 patients with NMO for the frequency of "secondary progression," as defined by continuous objective deterioration without remission over more than 12 months after one or more attacks. They found that secondary progression was rare in relapsing NMO despite the fact that NMO has a higher attack frequency, and patients tend to be older than those with MS. In contrast to MS, in which attack-free secondary progression accounts for most neurologic impairment, NMO disability was found to be related to clinical relapses (12).

RECLASSIFYING JAPANESE OPTICOSPINAL MULTIPLE SCLEROSIS AS NEUROMYELITIS OPTICA

One of the major points proposed by the Mayo group is that Japanese patients with the opticospinal variant of MS be reclassified as having NMO (13,14). In the Japanese opticospinal variant of MS, one does not see a DRB1*1501 (DR2) haplotype association as is seen Western MS. Instead, the DPB1*0501 allele has been reported to occur in 90% of the Japanese population with opticospinal MS compared with 60% of Japanese control subjects (1). The Japanese patients with opticospinal MS have severe attacks associated with optic neuritis and longitudinally extensive cord lesions, lack oligoclonal bands in the CSF, and have a generally poor prognosis. Nakashima et al (15) noted that the IgG1 subclass of IgG is not detectable in the CSF of patients with NMO but is elevated in patients with MS. This IgG contributes to the oligoclonal bands seen in MS but not in NMO.

Anecdotal reports suggest that interferon β is not therapeutically effective in opticospinal MS or in NMO but that immunosuppressive drugs may be helpful (4). Cree et al (2) have recently reported that, compared with Caucasian Americans with MS, African Americans have a greater likelihood of developing opticospinal MS and transverse myelitis and have a more aggressive disease course. It would be interesting to know whether these patients are seropositive for NMO IgG.

LUPUS ERYTHEMATOSUS, SJÖGREN SYNDROME, AND THE NEUROMYELITIS OPTICA ANTIBODY

Pittock et al (16) and Weinschenker et al (17) have identified an NMO-like disorder in some patients with SLE and SS and in some patients who are antinuclear antibody (ANA)-positive or extractable nuclear antibody (ENA)-positive without fulfilling the clinical criteria for SLE or SS. These patients have optic neuritis and extensive spinal cord lesions and are NMO IgG-positive. Pittock et al (16) tested serum samples from patients with NMO (79), recurrent longitudinally extensive transverse myelitis (rLETM) (44), SLE (2), and SS (14) for NMO IgG, ANA, and ENA. Approximately three fourths of patients with NMO and rLETM were NMO IgG-positive. Half of these patients were also ANA-positive and about one seventh were ENA-positive. Most did not fulfill the clinical criteria for SLE or SS. There was a higher frequency of nonorgan-specific autoantibodies in NMO IgG-positive patients than in NMO IgG-negative patients. Nonorgan-specific autoantibodies may reflect a more intense autoimmune response.

In a similar study, Weinschenker et al (17) tested, under masked conditions, the serum of 38 French patients for NMO IgG. Five had uncomplicated SS, 5 had uncomplicated SLE, 8 had uncomplicated NMO, 6 had NMO with either SS or SLE, 8 had isolated and/or recurrent optic neuritis or myelitis with SS or SLE and 6 had SS with neurological disorders other than optic neuritis or myelitis. NMO IgG was detected only in patients with optic neuritis or myelitis. NMO IgG positivity was associated with NMO or NMO partial syndromes in patients with SLE and SS but not with systemic autoimmune as seen in uncomplicated SLE and SS.

MRI IN NEUROMYELITIS OPTICA

The issue of brain MRI lesions in NMO has been controversial. Rocca et al (18) added magnetization transfer and diffusion tensor sequences to conventional MRI in the examination of 10 patients with NMO and 15 control subjects. On conventional MRI, no macroscopic T2-visible brain lesions were seen in the control subjects or in 6 (60%) of the patients with NMO. Two patients with NMO had one T2 lesion each, and 2 had a few nonspecific T2 abnormalities thought to be age-related. But all 10 of the patients with NMO had abnormal proportions of bound and free protons (decreased magnetization transfer ratio) and increased mean diffusivity within their normal-appearing gray matter, suggesting the presence of tissue damage in areas where conventional T1 and T2 imaging showed no abnormalities.

Pittock et al (19) addressed the issue of conventional MRI lesions in NMO in a study involving 60 patients with the diagnosis of NMO on the basis of Wingerchuk's 1999 criteria (See above). Brain MRI lesions were detected in 36 (60%). Most were nonspecific, but 6 patients (10%) had MS-like lesions, usually asymptomatic. Another 5 patients (8%), mostly children, had diencephalic, brainstem, or cerebral MRI lesions atypical for MS. One patient had large cerebral lesions and was comatose. The other patients had subtle lesions. In a large percentage of patients, the MRI brain lesions localized to the sites of high aquaporins protein concentration: the spinal cord, optic nerves, hypothalamus, and periventricular region (8). If Pittock et al (19) are
correct, a substantial percentage of patients with NMO are
being misdiagnosed as having MS.

REVISING THE DEFINITION OF
NEUROMYELITIS OPTICA

Based on this work, Mayo Clinic researchers have
proposed a revision of the previously published criteria for
the diagnosis of NMO (3) that had included three absolute
requirements: optic neuritis, acute myelitis, and no clinical
manifestations implicating other CNS regions. The pro­
posed new criteria (20, 21) are optic neuritis, myelitis, and
at least two of three supportive features: 1) MRI evidence of a
contiguous spinal cord lesion extending over three or more
segments at clinical disease onset; 2) brain MRI signal
abnormalities not typical for MS, that is, not involving the
periventricular region and not scattered in the white matter;
and 3) NMO IgG seropositivity. According to these criteria,
brain imaging abnormalities found outside the optic nerves
are compatible with NMO. Also compatible with a di­
agnosis of NMO are unilateral optic neuritis alone and optic
neuritis and myelitis occurring weeks or even years apart.

The Mayo Clinic efforts to characterize NMO have
been criticized because they do not fit the original 19th
century clinical description of the disorder (22). Depending
on one's point of view, these studies, taken together, display
the asset of internal consistency or the liability of circular
reasoning. Critics will need to supply contradictory data.
Until that time, the evidence stands in favor of keeping an
open mind and considering a new approach to the diagnosis
of Devic disease.

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Simmons Lessell
The Gaon of Neuro-Ophthalmology

Jonathan D. Trobe, MD

“Gaon” is the Hebrew word for “learned one.” In past times, a gaon was a rabbi of exceptional erudition who was asked to settle difficult religious questions referred to him by Diaspora Jews. Simmons Lessell, born 73 years ago in Brooklyn, New York, is not a rabbi. But to his former fellows and to others who have encountered his teachings, he is a gaon. It has been said that there are two kinds of American neuro-ophthalmologists: those trained by Lessell and those who wish they had been trained by Lessell. His former fellows, many of whom are now the oligarchs of neuro-ophthalmology, declare that he cannot be stumped and that he has a funny story for every diagnosis (“for every lesion, a line”). His written contributions to the neuro-ophthalmic literature are extraordinary. In more than 40 years on the job, Lessell has produced over 200 publications, elevating the case report to a high art. His descriptions of toxic optic neuropathy, cerebral achromatopsia, palinopsia, indirect optic nerve trauma, and idiopathic pachymeningitis are examples of the most luminous prose in the medical literature. Last year he retired as director of the Neuro-Ophthalmology Service at the Massachusetts Eye and Ear Infirmary, but he continues a vigorous practice of neuro-ophthalmology and was recently named the Paul A. Chandler Professor of Ophthalmology at Harvard Medical School.

This interview took place in his office on October 28, 2006.

JDT: And your mother?
SL: Came from Bessarabia, on the Ukrainian-Romanian border, of a very poor family. In Bessarabia, they had dirt floors, like in Fiddler on the Roof. After her father served in the Russo-Japanese War at the beginning of the 20th century, the family escaped to New York. Even in the United States, they were poor. I recently came across a photo of my mother’s mother chopping up a chicken behind the counter of a butcher shop.

JDT: How did your parents meet?
SL: At a Jewish home for the aged benefit dance. My father, impetuous in many ways, dragged her into an alley and put a ring on her finger. It was his mode of asking for her hand.

JDT: How was this match received?
SL: Ohhh, for a German Jew to marry someone of Russian Jewish background was not done....

JDT: Tell about the neighborhood in Brooklyn.
SL: We lived in a little walk-up behind my father’s dental office. The people were about 85% Sicilian. There...
FIG. 2. Camping at age 8, Camp Nimrod, Livingston Manor, New York, with sister Florence (left) and a friend, 1941.

was a small Jewish community and, of course, two synagogues....

JDT: Why two synagogues?
SL: So you could say you would never be seen dead in the other one!

JDT: How did you get named “Simmons”?
SL: My father’s father, who had died before I was born, was Simon. They were going to name me after him, but someone said they would call me “simple Simon.” One of my relatives suggested “Simmons” to keep my Hebrew name of Shimon. My mother used to ask me if I liked the name. And I said I liked it fine. The only other Simmons I know is the son of one of my former fellows, who is named after me! By the way, when I was growing up, I was so skinny that everyone but my wife and parents called me “Bones.” My wife says that when I met her, I stood 6 feet tall and weighed 128 lbs.

JDT: In your childhood, did you go to synagogue?
SL: Yes, it was an old-fashioned orthodox schul. One of my clearest memories is from Yom Kippur in about 1944 (many men were in military uniform). From the center of the synagogue, they would announce the contributions to the synagogue. “Mr. Moskowitz from Moskowitz’s Hardware—$20.” A respectful murmur would go through the congregation. “Shapiro from Shapiro’s Drug Store—$15.” Another murmur. “$5—anonymous.” (Laughs) I can reconstruct every detail from that era. It was like a Woody Allen movie.

JDT: By this time, had you already discovered that you were smart and funny?
SL: I suppose so. Where I grew up, you either had to be strong, which I wasn’t, or run fast, which I couldn’t, or else laugh your way out of it, which was my defense. By the way, being smart was a distinct disadvantage.

JDT: The neighborhood was that bad?
SL: It was rough. I think there was a protection racket in kindergarten. The local high school was terrible.

JDT: Did you try to avoid it?
SL: Yes, luckily I was accepted at a magnet science school in Manhattan: Stuyvesant High School. It was arguably the best high school in America.

JDT: What made Stuyvesant High School so good?
SL: First, you were not there unless you were interested in studying. There was no contamination by disruptive students. Second, it was the Depression, and teachers with advanced degrees could not get jobs at the college level. So we had lots of PhDs as teachers. I most remember my chemistry teacher, Thomas Blue. He was the first exciting teacher I ever encountered. I wanted to emulate his style. He used humor freely and didn’t take himself seriously.

JDT: From Stuyvesant, it was Amherst College. Why?
SL: Mr. Hart, the assistant headmaster at Stuyvesant, had gone to Amherst. My sister Florence, who is 3 years older than I am, was dating someone who had gone to Amherst and seemed very sophisticated at the age of 24. He said that Amherst was the best college in America.

Mr. Hart thought it would be a great place for me to go, and he offered to write me a letter of recommendation. I was accepted without an interview! I arrived at Amherst by train with a big trunk, never having been out of New York State. I walked about utterly stunned by the beauty of the surroundings. I felt I was in a foreign milieu.
JDT: What was foreign?
SL: It was culture shock for a Jewish boy from Brooklyn. I would stay up late at night writing letters to my parents as if I had landed in the central highlands of New Guinea and was describing the habits of other tribes. Everybody drank—heavily. A huge proportion of my classmates came from divorced families. I had not known a single divorced family in Brooklyn. Many of my fellow students were children of celebrities.

One of my roommates was the son of Drew Pearson, the famous columnist. We public school graduates, who were probably in a small minority, were not as well prepared academically as the students from prep schools. They had been taught how to think and write critically and we had not. But we caught up by the second year.

JDT: Ethnic diversity?
SL: Well, among 360 students in my class, there were two African-Americans—put in the same room. There were two Asians, both from Japan.

JDT: But your recollections of Amherst are positive?
SL: Very. My kids say I just remember the good parts, but my wife Irma, who spent a good deal of my last three years there with me, remembers how fine it was.

JDT: When and how did Irma enter your life?
SL: I met her on a blind date in Great Neck, New York, where she lived. I decided immediately that I would marry her. And it has worked for 55 years.

JDT: Did any course of study strike your fancy at Amherst?
SL: Vertebrate paleontology, which is just descriptive biology. You can’t do much experimentation. The main variable is time—huge chunks of time, reflected in geological strata. For my undergraduate senior thesis, I spent a summer collecting fossils in Muddy Gap, Wyoming, population 3. I described some previously undescribed species, one of which I named after my wife: *Perignathus irmaei*. And then it came time to apply to medical school.

JDT: Why medical school?
SL: I had decided early on. My parents thought it was a wonderful idea. My father encouraged me—well, really pushed me. I’m not saying he wouldn’t have supported me if I had done something else. Anyway, I applied to Cornell, NYU, Yale, and Columbia and went to Cornell.

JDT: What medical school experiences shaped the direction of your career?
SL: In medical school, I realized that I was not interested in treatment. Treatment is ephemeral. Think back
to when you were an intern. They are not using most of those medications anymore. I don't know an alternative to using whatever is current, but you know it is going to be displaced. For example, you know that Avonex will not be used 20 years from now for multiple sclerosis. It will be supplanted. Physical diagnosis and pathology are forever.

JDT: How did you do at Cornell Medical School?
SL: Well, I was not much of a class attendee. Things went along fine until biochemistry. The professor was a Nobel laureate for discovering oxytocin. But one of his other achievements was discovering a minor vitamin. The exam was all about vitamins. I was called in by the course director and told that I had done poorly. I explained that I didn't go to class. I said that I synthesized things from my reading and hadn't thought vitamins were very important. To my surprise, he said, "Don't change your system."

JDT: I am astounded that after doing poorly on an exam, you would be so bold with the professor and yet be affirmed.
SL: Well, that's how Cornell was. It was a welcoming place.

JDT: Where does ophthalmology come in?
SL: In the second month of anatomy, into class walks the youngest member of the ophthalmology faculty, who says: "This is a good time to learn which way the eye muscles move the eye." He was spellbinding. His name was Ed Norton. He had gone to Cornell Medical School and taken a year of neurology training before going into neuro-ophthalmology. I decided right then that I would emulate Ed Norton. Not long afterwards, he wrote me a letter of recommendation for an eye residency. And 25 years later,
FIG. 7. With Irma during his internship at Bellevue Medical Center, New York, 1958.

he spoke on my behalf when I was nominated to the professorship of ophthalmology at Harvard.

JDT: But you decided to do neurology first?
SL: Yes, I thought—like Norton—that you needed a perspective; not a full neurology residency, perhaps, but the first year, which teaches you how to think about localization, what the diseases are, and how to do the examination. So I went after a 1 year appointment. I was roundly ignored by several programs. But I was finally directed to Dr. George Schumacher, who had been chief of neurology at Cornell-Bellevue and was now chief of neurology at the University of Vermont. Schumacher accepted me for a year and it was the best year of my entire graduate education. Now in his mid-90s, Schumacher was—and is—an extraordinary man. He is thorough and honest, a paragon. And he stimulated my interest in fishing, my favorite hobby. Until recently, I would sometimes fly him down to Boston to attend medical conferences with me and then we'd fly to Florida together to go fly fishing.

To give you an idea about Schumacher, here's a story.

When Schumacher was about 88, we attended brain cutting together at the Massachusetts General Hospital, run then by E. P. Richardson, the renowned neuropathologist. The medical student always spoke first, then the residents, and finally C. Miller Fisher, MD, the great Harvard neurologist. We were each asked to localize the lesion and give our reasons. On one occasion, before cutting the brain, everyone, including me, predicted the lesion would be below the tentorium. Schumacher said it was above the tentorium. Miller Fisher agreed with Schumacher. I said to myself, “Here is a great gentleman. He probably knows that the lesion is below the tentorium but he does not want Schumacher to be embarrassed.” Well, the lesion was above the tentorium and they were the only ones who were right!

JDT: What about Vermont?
SL: It was a little boutique of neurology. Each patient was examined in phenomenal detail. When it was over, I knew I still had my military duty, so I looked for a way to meet my service obligation and get more neurology.

JDT: And you solved this by....
SL: Going to the National Institute of Neurological Diseases and Blindness in 1960. They put me in the Epidemiology and Genetics branch with Leonard Kurland, who later conducted the wonderful neurologic epidemiology
Of all the wonderful things I learned from Simmons Lessell, the most important is that a satisfied soul is born of a generous spirit.

Mark Borchert, MD

He is equally eager to tell you a joke, discuss why the Red Sox lost the pennant, and quote an obscure journal article that appeared in the German literature. He gets to know each of his fellows in a deeply personal way. By the end of the fellowship, you feel as if you just spent a year with your grandfather. I grew more professionally and personally in that 1 year than in any other year of my life. Although the details are a blur, I remember laughing and loving every day of it.

Dean Cestari, MD

Each working day was constantly spent in Simmons’ company ("You go wherever I go; you’ll know when I’m happy, you’ll know when I’m sad."). There was the endless personal generosity that he and his wife Irma gave to the fellows and their families, his passion for the critical importance of the clinical history ("If you don’t know the diagnosis by the end of the history, you are in diabolical trouble.") , the 16-foot lanes, the limitless supply of stories, jokes, and aphorisms, all accompanied by accurate rendition of appropriate accents—except Australian, which he never mastered. There was the passionate search for that elusive reference ("He who ignores the old German literature will discover many new syndromes."), trooping to the library just for the fun of looking up who wrote what in the Lancet exactly 100 years ago, matching diagnostic wits with neuroradiologists ("the shadowkings") or neuropathologists, and always, every day, paying for lunch for his fellows ("When your income is bigger than my tax return, you can buy lunch.").

Jon Currie, MD

He is not only the smartest man that I have ever met, but also the funniest! A year ago my (now) wife and I were trying to think who should marry us. Due to his importance in our lives, we asked Simmons, and he agreed. He got ordained in the Universal Life Church online and became the first Jewish reverend!

Robert Egan, MD

FIG. 10. With former fellows at NANOS Meeting in Copper Mountain, Colorado, in 2005. From the left: Robert Egan, MD, Valerie Biousse, MD, Michael Lee, MD, Nicholas Volpe, MD, Marc Dinkin, MD, Joseph Rizzo, MD, Dean Cestari, MD, Misha Pless, MD, Steve Hamilton, MD, Judith Warner, MD, Mark Borchert, MD, Irma Lessell, MD, Susan Pepin, MD, Nancy Newman, MD, Leonard Levin, MD, PhD, David Newman-Toker, MD, Jonathan Kim, MD, Howard Pomeranz, MD, PhD, and Alfredo Sadun, MD, PhD. Former fellows not present: Michael Cohen, MD, James Coppeto, MD, Robert Gise, MD, Jon Currie, MD, Barrett Katz, MD, Neil Snebold, MD, Nancy Weiner, MD, Charlotte Thompson, MD, Glenn March, MD, and Michelle Banks, MD.

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What the Fellows Remember

At least once a week, I would look up an esoteric word in the dictionary, convinced that I had finally found a deficit in his vocabulary, but he would prove me wrong time after time. Toward the end of my fellowship, I finally stumped him with the word, “luthier,” but only because I knew he wasn’t a guitar player like me.

Simmons not only invited me to his home for dinner on numerous occasions, he took me on guided fishing trips to the ocean, the local lake, and even to Florida. How many fellowships include a guided trip to Lake Okeechobee to fish for largemouth bass? I must have brought him good luck, because he caught the largest bass of his life on one of those trips. The most indelible image of my year with Simmons is a warm Spring afternoon when he presented me with a brand new fly rod and proceeded to teach me how to cast in the parking lot of the Massachusetts Eye and Ear Infirmary.

Jonathan Kim, MD

As his fellow, I was in his “back pocket.” It was the best year of my educational life. He treated me with great respect and gave me great independence. My desk was in his office and I saw his life from all different angles. I enjoyed getting to know this man not only as a mentor and colleague but as a friend.

Michael Lee, MD

Watching Simmons unerringly tunnel in on what turned out to be the correct diagnosis was always a treat. Even better was the daily word play, which was fields more difficult than producing a differential diagnosis. But best was being mentored by a mensch—generous, honest, straighter than a meridian, approachable but never crossed.

Leonard Levin, MD, PhD

He found the best thing in each of his fellows and made us feel special, like an excellent parent with many different children. He taught me how to write and how to love writing. His command of the English language, both written and spoken, was extraordinary. He is a consummate clinician and an extraordinary wit. He loves and knows all show-tunes, but gets the words wrong!

He is teacher, colleague, father, and best friend.

Nancy Newman, MD

Simmons is one of the few people I’ve met in medicine who would rather say, “I don’t know what it is,” than make up a clever, hand-waving explanation that couldn’t possibly be proven or disproven. To hear that statement coming from someone with such vast knowledge and experience was simultaneously humbling and inspirational. Of many lessons I learned during my fellowship, this one about humility in the face of ignorance was perhaps the most profound.

David Newman-Toker, MD

The year I spent with him was the best year of my life. He was unselfish in his time, energy and attention, honest, succinct, and uncompromising in quality and ethics. The aspect I relish, remember, still glow about, is his treating me with respect, like an equal, while teaching me valuable aspects of the subtlety of the clinical exam. I miss him every day now that I’m on my own.

Susan Pepin, MD

The happiest, most salient moments were discussions on history and music. There were the endless conversations about opera plots and librettos, and the lectures on the origin of a word or the denouement of a particular historic battle. I’ll always remember his sayings:

“Do it with alacrity and utmost clarity.”

“It is much easier to be an editor than a writer.”

“There is no such thing as a ‘trace APD.'”

“Say ‘Man, woman, boy, girl.’” (Not gentleman, lady, male female.)

“Affability, Ability, Availability—the 3 A's that lead to success in professional life.”

Misha Pless, MD

The camaraderie with Simmons and other faculty, fellows, and residents at the Massachusetts Eye and Ear Infirmary was extraordinary.

We would help keep his examining room prepared by making sure the Goldmann perimeter was calibrated, that the visual field recording paper was always in stock and positioned properly in the perimeter, and that there were an ample number of cotton applicators with the cotton pulled out to a fine tip to test corneal sensation.

Howard Pomeranz, MD, PhD

After 24 years of working with Simmons, I am still learning from him!

Joseph Rizzo, MD

Simmons loves to laugh and to make others laugh. He had at least two jokes that he would present to his residents and fellows every day. They could be erudite or earthy. Humor was his way of showing his delight in how humans could be humans. Of course, the biggest laughs came from real life. These stories became a bond between mentor and mentee. I’ve enjoyed recounting these stories ever since.

Alfredo Sadun, MD, PhD

Simmons said when I accepted his offer of a fellowship, his goal was for the fellowship to be the best year of my academic career. It was.

Judith Warner, MD
studies in Olmstead County, Minnesota, for the Mayo Clinic. They sent us to the Epidemiology Intelligence Service course at the Center for Communicable Diseases in Atlanta and then for 2 years to the research station on Guam. After World War II, when we took charge of this vast expanse of tiny Pacific Islands, the United States government also took on the responsibility of medical care there. I was the only neurologist on an island with a population of 30,000 people—military and civilian. I had an EEG [electroencephalography] lab. I did arteriograms. I did pneumoencephalograms. I even did autopsies. With Asao Hirano as my neuropathologist, I wrote my most cited paper, “The Neuropathology of Parkinsonism Dementia on Guam” published in *Brain*.

**JDT:** What about the eye residency?

**SL:** I already had that—at the Massachusetts Eye and Ear Infirmary. You know the old story about the guy who applies to medical school and when he goes for his interview, they ask him why he wants to go to medical school. He says, “I have to. I already have an eye residency.”

**JDT:** Why the Eye and Ear Infirmary?

**SL:** Someone had told me it was the best residency. And I had read Dr. David Cogan’s book, *The Neurology of the Ocular Muscles*. But there were many, many applicants. Imagine, then, my surprise when I got the telegram telling me I had been accepted. When I arrived at the Infirmary in 1962, I worked in a lab with Dr. Toichiro Kuwabara on retinal glial cells. I learned histochemistry and continued it throughout my residency.

**JDT:** How was neuro-ophthalmology nurtured during your eye residency?

**SL:** Cogan had a tiny examining room near where I was working. He would show me cases. As my residency was ending, I went to him to get his advice about neuro-ophthalmology fellowships. He said, “Well, Simmons, a
neuro-ophthalmologist is someone who other people think is a neuro-ophthalmologist. And people think you are a neuro-ophthalmologist. You don’t need a fellowship.”

JDT: Why did Cogan think that?
SL: Because people were sending me private cases to look at even as a resident.

JDT: And what happened next?
SL: Before I had finished the residency, Ephraim Friedman, a very junior faculty member and the fair-haired boy of the Infirmary, called me in and said, “They’ve just picked me to be the chair of ophthalmology at Boston University. Would you join me?” I hesitated for a nanosecond and then went over to B.U. as the neuro-ophthalmologist!

JDT: Is that when your time at Boston City Hospital began?
SL: Yes, I became director of the B.U. ophthalmology service there and sat on the Executive Committee with Derrick Denny-Brown, chief of the Harvard neurology service there, who had earlier refused me a 1 year neurology position. I remained at B.U. for 18 years.

JDT: When did you begin training neuro-ophthalmology fellows?
SL: I took on a few while I was at B.U.—Michael Cohen, Robert Gise, Jim Coppeto, Alfredo Sadun, Jon Currie. At first I did not think there was a great need for neuro-ophthalmologists and that there were very few places where they should be trained. I did not think I could offer as much as, for example, Bill Hoyt. But there were some who, for logistical reasons, wanted to stay in Boston and so I took them on. Some wonderful people. At the end of their fellowship, I would send them out for a time with Hoyt. Hoyt and Miller Fisher had become part of my superego. I still ask myself, “What would they say about what I’m doing or saying?” I had begun to have more and more contact with Hoyt.
JDT: How?
SL: Here and there at meetings. Mutual interests. Correspondence. We even published papers together, on brainstem arteriovenous malformations and the first paper on malignant gliomas of the anterior visual pathway.

I'll tell you about the genesis of that paper on gliomas. At one of the early Walsh meetings, when they were still held at Hopkins, I presented a case of glioblastoma of the chiasm. Walsh attacked me, which is like having a Quaker make war on you. This nice man was saying there is no such thing. Then Hoyt got up and, a little more in character, insisted, "These are not malignancies; they're benign, hamartomatous lesions." Within 6 months, I had a second case of malignant glioma of the chiasm! I wrote to Hoyt and said, "Ha, ha! It's a real entity." He wrote back that he'd since seen one. So together we wrote up the three cases as malignancies.

JDT: How did your term at B.U. come to an end?
SL: In 1983 I got a call from Claes Dohlmann, the chief of ophthalmology at the Infirmary, asking me if I knew anyone who might be interested in the neuro-ophthalmology position because Shirley Wray, who occupied it, was moving over to Mass General. I gave him a list and then he said, "How about you?" And so I finally returned in 1984 to where I had done my residency. I've been here now for 22 years.

JDT: Was the transition an easy one?
SL: Well, getting appointed wasn't simple. There was one member of the search committee who was opposed to me. When I was called before the committee, I was sure I'd be asked why I wanted to come to Harvard. I was going to tell them, "I've always wanted to get a Harvard Coop card." [Editor: to get a card for the Harvard Cooperative Society, which administers the noted store in Harvard Square, you must be a student or faculty member at Harvard.] Anyway, he promptly asked, "Are you the world authority on anything?" I believe he saw his responsibility to be the guardian of science at Harvard. He later made an appointment to come to my lab on a Saturday morning. He spent hours looking over my papers and quizzing me about the research behind them. Apparently he wrote a negative report about me. So they had to call in two witnesses on my behalf—Ed Norton, who came up from Miami, and Norman Geschwind, who...
was the James Jackson Professor of Neurology at Harvard and had earlier been chief of neurology at B.U.

JDT: Had Geschwind influenced you?
SL: Absolutely. An extraordinary man. Often wrong, but so stimulating, so provocative. The cognitive functions group at the Boston Veterans Hospital, who were faculty at B.U., included not only Geschwind, but Frank Benson, Edith Kaplan, and Harold Goodglass. For me, it had been like landing in heaven!

JDT: And when you came over to Harvard, you began taking fellows regularly....
SL: Yes, Joe Rizzo was the first. He never left. He has gone on to be a great experimentalist with a terrific imagination. But I do not want to slight any of my fellows. They have all been great.

JDT: As you look back, do you consider the fellows your greatest achievement?
SL: Well, teaching in general—to fellows, to residents, to medical students. There is an old expression: those who can, do; those who can't, teach; those who can't teach, teach teachers. I'd like to think I've given the lie to that expression. Look how many of the former fellows have become extraordinary teachers. Several of the first teaching awards given by the academies of ophthalmology and neurology went to my former fellows Nick Volpe, Alfredo Sadun, and Nancy Newman.

JDT: And now?
SL: I'm still doing it—teaching and seeing patients. I'm still excited by it. I'm excited about that bust in the conference room.

JDT: What bust?
SL: Ephraim Friedman, who sculpted a bust of Cogan, did one of me. The Infirmary's Board of Trustees decided to buy one and put it in the Infirmary auditorium.

JDT: It is the only bust in the auditorium?
SL: Yes.

JDT: What is special about your teaching?
SL: I'm honest. I acknowledge my shortcomings. I've also tried to be generous. If you have more pieces of the puzzle than the person you are teaching, the next criterion is generosity. What you are trying to do is to give to someone else everything that you have acquired and the means of gaining more. You hope that each one will do even better than you do. The teacher who holds back or is abusive or gruff—I do not see a place for that. And then, be yourself. At meetings, I see people trying to be funny when they aren't funny. They double project with cartoons and then all your attention is taken up with trying to figure out the joke. If you have a good sense of humor, use it. But it doesn't fit everybody.

JDT: Among your academic contributions, what do you value most?
SL: I don't think I've made any great academic contributions.

JDT: But many of your papers are gems of medical writing.
SL: Well, when I started out, I did not write very well. Cogan was helpful there. He was a natural writer. One draft. And I got advice from Stanley Robbins, whose Textbook of Pathology was once the best seller among medical textbooks. He said, “There is no great writing, just great rewriting.” And I think he’s right. Also, you learn to write by writing and by reading. I fear that one of the reasons that most writing is not good is that writers aren’t reading.

JDT: And what paper would you pick to talk about, it would be....
SL: The one I just published with Jonathan Kim about the superimposition of the age-related depletion of
axons on a static optic neuropathy. This applies to people who early in life suffer a vision-limiting optic neuropathy that is stable for decades and then begin to lose vision. You work them up from top to bottom and find nothing. Why are they losing vision? My theory is that it is like the post-polio syndrome: the tiny depletion of axons with age normally has no impact. But if you start out with 5% of your original complement, then you’re in trouble. I think that the first sentence of that paper is one of the best things I’ve ever written: “The tacit assumption that progression or recurrence of an optic neuropathy results from the same mechanism that inaugurated the disorder has tended to obscure the possibility that in some cases these phenomena might have a pathogenesis independent of the original.”

I’m also fond of an editorial I wrote in the Archives of Ophthalmology entitled “Ischemic Optic Neuropathy: Enigma Variations.” [Editor: Enigma Variations is the title of a musical composition by Elgar.] In that editorial, I quoted two authors. Richard Feynman wrote in 1998: “I believe that to solve any problem that never been solved before, you have to leave the door to the unknown ajar.” Wisława Szymborska said in his Nobel Lecture in 1996: “This is why I value that little phrase ‘I don’t know.’ It’s small, but it flies on mighty wings.” The gist is that we don’t know what causes ischemic optic neuropathy and knowing will only come with accepting that we do not know.

JDT: Any regrets about choosing neuro-ophthalmology as a career?

SL: Absolutely none. What I do regret is that it is going to be almost impossible for anyone in the coming generation to have the kind of career that you and I have had.

JDT: Why?

SL: Accountants are setting the priorities of clinical departments. The non-earners will not get sufficient support. There are departments that redistribute money, but it can only be done to a certain extent. Neuro-ophthalmology’s existence is in force threatened. Maybe neuro-ophthalmology will have to alloy with some gainful enterprise like strabismus or plastics.

Norman Geschwind used to say that the difference between being a clinician and an academician is time. Time to think, to consolidate, to read, to discuss. To be spared 40 patients in the waiting room. Psychiatry is the business of every physician. You cannot give that component when medicine is a quick, chief complaint-oriented experience. Will the patient be correctly diagnosed? Almost certainly. Will the patient get the correct medications, surgery, advice? Almost certainly. Will that fully satisfy the patient’s needs? Absolutely not. I think that most patients come to physicians with fears that go unexplored unless they are given time. What was Freud’s major contribution to medicine? It is that many patients need an hour with the doctor.

JDT: Despite this apocalyptic view of where neuro-ophthalmology and medicine are going, you are still training fellows at the same rate as you did earlier and they are finding jobs and I think they are practicing the way you taught them to practice.

SL: Well, many of them are doing other things besides neuro-ophthalmology.

FIG. 17. In his examining room at the Massachusetts Eye and Ear Infirmary with fellow Susan Pepin, MD, and resident Aisha Traish, MD, 2004.
JDT: In the 40 plus years of your career, what has changed about neuro-ophthalmology?
SL: I haven't changed my practice at all. Maybe I'm compulsive and stubborn, but I still do the same things. But I've had bosses who have permitted me to do that. It cannot go on much longer.

JDT: So when people come to you and say, “I am considering neuro-ophthalmology as a career,” what do you say?

SL: Go where your heart leads you. You will have to make some accommodations. But everything requires accommodations.

JDT: And what about you. Will you ever retire?
SL: I will tell you something a patient told me recently. She is from rural Maine. I asked her what town she was from, and she said, “I come from far away. It's not the end of the world, but you can see the end of the world from where we live.” At age 73, I do not have a 30 year plan.

FIG. 18. Punctuating a crucial moment in a story by sounding the drum and cymbals (gifts from the MEEI residents), in his MEEI office, 2006.

The Neurology of Eye Movements,
4th Edition
R. John Leigh, MD, FRCPC and David S. Zee, MD.

Scope: This is a major revision of the classic text on everything you would want to know (and more!) about ocular motility. The first edition of this remarkable book was published in 1983 at 281 pages, and this fourth edition at 763 pages plus an accompanying DVD reflects the veritable explosion of information on the neurobiology and clinical relevance of eye movements. The authors are the same duo of clinician-scientists whose names have literally represented the study of ocular motility for more than a quarter century.

As in the first edition, the book is divided into two sections, the first dealing with fundamentals of neurophysiology of eye movements and the second dealing with its clinical applications. The first eight chapters present the results of basic ocular motor research in a form useful for clinicians. The reader will find an unparalleled up-to-date synthesis of neuroanatomy and neurophysiology of ocular motility. The last four chapters provide a pathophysiologic approach to clinical disorders with symptoms and signs of eye movement disorders, including the differential diagnoses of disorders involving the muscles, neuromuscular junction, ocular motor cranial nerves, vestibular system, and central nervous system areas involved in ocular motility.

Each chapter begins with an outline of its content for easy reference and ends with a summary in bullet-point form, followed by extensive, comprehensive referencing. Throughout the chapters there are multiple summary boxes, figures, schematic diagrams, and tables.

The accompanying DVD provides the full text of the book with links to 23 video displays that provide downloadable teaching slides. Additionally, the DVD contains 200 video clips, images, and the hand-written lecture notes “Linear Control Systems in the Oculomotor System” by David A. Robinson, the acknowledged mentor of the authors.

Strengths: This is the most meticulously researched study of eye movements to be found in a single monograph, written by the grand masters. It is comprehensive in scope and in referencing. Many of the fine drawings and diagrams have been retained, and new ones have been added. New attempts to highlight key points are quite effective. The DVD is simply amazing!

Weaknesses: The density of the material presented can be overwhelming. To read this book cover-to-cover takes fortitude, but it is well worth the effort. Compared with other texts, images are less plentiful, and some CT scans probably should have been retired. See if you can find the upside-down MRI!

Recommended Audience: This book is a “must” for neuro-ophthalmologists, neuro-otologists, and basic scientists whose work involves ocular motor systems, and for every medical and biomedical engineering library. It is the reference for any medical student, resident, and physician who sees patients with ocular motility disorders and for the growing number of clinical and basic science researchers using eye movements as experimental tools in brain research.

Critical Appraisal: This book is the “last word” on ocular motility, written by the foremost experts in the field.

Nancy J. Newman, MD
Emory University School of Medicine
Atlanta, Georgia

Neurological Therapeutics Principles and Practice, 2nd Edition

Scope: This is a mammoth production that aims to cover all of neurologic therapeutics. It is the second edition of a two-volume work that appeared 3 years ago and won the First Prize in the British Medical Association Book Competition. It has grown to a three-volume set of nearly 4,500 pages. Dr. Noseworthy, the noted Mayo Clinic neurologist who specializes in multiple sclerosis, is again the editor-in-chief. There are 14 sections, each with its own editor—and each a very big name in the field. Each section has about 20 chapters, each written by a big name—actually 360 names. Most of the authors from the first edition have been retained. They have updated and often amplified their chapters.

Neuro-ophthalmology is supervised by Dr. James Sharpe, a respected Toronto neuro-ophthalmologist specializing in eye movement disorders. His domain is nine chapters: optic neuropathies, papilledema and idiopathic intracranial hypertension, chiasmal and retrochiasmal disorders, pupal disturbances, ocular motor nerve palsies, nystagmus and saccadic disorders, gaze disorders, ocular myasthenia gravis, and cavernous sinus disorders.
Strengths: The emphasis on therapeutics is what distinguishes this work from the major textbooks of neurology. Neurologic therapeutics, which to skeptics may be an oxymoron, never looked so impressive. The editors have generally kept a tight rein on the writers to prevent them from indulging in excessive, impractical verbiage. Their chapters are succinct, authoritative, and readable. They start with a brief theoretical background and finish with a big bang on how to manage the patient. The production values—text font, layout, and illustrations—are impeccable. The references are ample and reasonably up-to-date. The indexing is complete. The neuro-ophthalmic chapters provide a well-reasoned and concise take on their subjects.

Weaknesses: This is a hernia-inducing tome. Forget portability. At a few pennies shy of $500, it is an investment. Such a high-priced giant may seem like a dinosaur to those who now rely on on-line sources, which are approaching high quality, are more easily updated, and are just a few clicks away on a screen.

Recommended Audience: Physicians in training and physicians in practice—of any specialty that touches on neurology—will benefit from this book.

Critical Appraisal: For those who have a sturdy bookshelf and are seeking a concise statement on a neurologic condition and in particular an authoritative, scientific approach to treatment, this is the go-to source. It may be expensive and hard to read on the fly, but a book like this is more expertly put together than the typical on-line reference.

Jonathan D. Trobe, MD
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Neurological Differential Diagnosis—A Prioritized Approach


Scope: This text, authored by three clinicians, attempts to provide a problem-based differential diagnosis for the full spectrum of neurologic disease. The intended audience includes medical trainees, especially neurology, neurosurgery, and psychiatry residents, as well as internal medicine and family practice residents, medical students, and primary care physicians.

Following the initial two sections that review neuroanatomy, neuropathology, and clinical syndromes, the text reviews the differential diagnosis of vascular insults, paroxysmal disorders, neuropsychiatric disorders and dementia, movement disorders, infectious, inflammatory, and demyelinating diseases, peripheral neurology, pediatric neurology, neurogenetics, neuroradiology, spinal cord disorders, and diagnostic tests. The text ends with a section on clinical pearls, including a quick reference on emergency neurologic medications, warfarin and phenytoin dosing and indications, and neuroprognostication.

Strengths: The unique aspect of the book is that it attempts to prioritize neurologic differential diagnosis by listing the most common possibilities first. It also stresses less common diagnoses that can be potentially fatal or disabling. It is not a book of neurologic "zebras."

Weaknesses: There is a paucity of illustrations. The only images are pathologic slides of common entities. Having no neuroimages in a section on neuroradiology makes comprehension of the concepts difficult, especially if the reader is unfamiliar with imaging. Also there are no neuroanatomy diagrams, which would have been especially helpful in the neuroanatomy section and in the section on peripheral neurology.

Recommended Audience: This book would be most appreciated by neurology or neurosurgery residents and medical students on a neurology rotation. Internal medicine or primary care practitioners would also find this volume useful in their daily practices. It is probably too basic for experienced neurologists and neurosurgeons.

Critical Appraisal: Some sections are uneven in depth. However, overall the text succeeds in presenting a user-friendly guide to the most common and most potentially dangerous neurologic disorders.

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Stroke Care: A Practical Manual


Scope: Despite its small size, this book is a comprehensive guide for taking care of people with strokes. It is written by two internists and a geriatrician. It includes chapters on nursing and rehabilitation, stroke prevention, decisions on when to give and withhold care, and end-of-life care as well as the information you need to know when you are faced with a patient with an acute stroke or transient ischemic attack (TIA) in the emergency room or hospital ward. It is intended for "people who look after stroke patients, in particular doctors and nurses working in hospitals."
Strengths: There are many. The book is organized by the time course of diagnosis and treatment (what to do in the first few hours, days, and weeks). The information you need quickly is in easy-to-read tables. Stroke syndromes, tests, criteria for thrombolysis, drugs, and doses are all spelled out. Most of the stroke scales you need are in the appendix. The authors’ treatment advice is supported by randomly controlled clinical trials, which they summarize in highlighted boxes. There is even a table of abbreviations at the beginning of the book!

Weaknesses: The chief weakness, for American doctors, is that the book is written for an English audience. British drugs are called by their UK names (paracetamol, not acetaminophen), which can make this manual less practical for users in the United States. The most striking differences are in medical decision making. In England (but not in Scotland, as the book points out), “no one can give consent on behalf of adults who does not have the capacity to consent. They may be treated if it is in their ‘best interests’.” (Few Englishmen have advanced medical directives, apparently.) The physician may consult with the patient’s family before deciding what the patient’s best interests are, but the ultimate decision is his or hers. In the United States, we tend to share medical decision making with the patient’s family or the person legally empowered to make decisions.

Recommended Audience: Doctors who care for stroke patients will find this book very useful. Thoughtful physicians reading the book will realize that they need to work with nurses, therapists, family members, and social service agencies to obtain the best possible outcome. I am not sure there is enough in the book about nursing and therapy to appeal to other caregivers.

Critical Appraisal: If you take care of hospitalized patients with stroke, this book will help you. When you read the chapter on medical decision making, keep in mind the fact that different countries have different customs and laws.

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Color Atlas of Neuroscience: Neuroanatomy and Neurophysiology


Scope: This is a pocket atlas of neuroscience that provides an overview of neuroanatomy and neurophysiology. There are 194 color plates with accompanying text. The authors are basic scientists who have consolidated a wealth of information into a concise resource. The book is written for students of neuroscience to serve as an introduction to the complex subject matter, a supplementary resource for more detailed textbooks, and a study guide for examinations.

The book is divided into 12 sections: Basic Neuroanatomy, Embryology, Cellular Structures, Somatosensory System, Motor System, Brainstem, Autonomic Nervous System, Special Senses, Hypothalamus, Limbic System, Higher Brain Centers, and a final section on Damage and Repair. At the end there is also a brief reference list and a glossary of terms and comprehensive index.

In each section, the left side of the page provides details on structure, function, and physiology. The text is succinct, with key terminology in bold. On the right side of the page, there is an accompanying computer-generated color diagram with key structures and/or pathways highlighted. The figures are clearly labeled and color-coded.

Strengths: This is an ambitious work covering the entire range of neuroscience on macroscopic and microscopic levels. The authors have made complex material manageable and easy to absorb. Attention is given to the visual afferent system with detailed explanations of photoreceptor function and physiology as well as visual field defects with correlation to the retinal pathways. The visual efferent system is also described with respect to cranial nerve nuclei, extraocular muscle function, and the vestibulo-ocular system. The sections on the neuroendocrine and limbic systems are particularly well written. The autonomic nervous system section includes useful charts cataloging neurotransmitters, receptor subtypes, and target organs. The section on higher brain centers includes a brief review of molecular pharmacology of certain drugs and their use in particular disease states.

Weaknesses: Matching the text with its accompanying figure often requires searching and can be time-consuming; labeling by number of both text and diagram would have been more straightforward and helpful. Although the computer graphics are of high quality, additional images depicting histopathology, cadaver dissections, and neuroimaging are not included. The section on embryology is too brief. Several clinical correlations are made to disease states, but they are few.

Recommended Audience: This color pocket atlas is ideal for those interested in neuroscience who are also looking for a quick reference guide for the central and peripheral nervous systems. It is by no means an exhaustive, highly detailed atlas, although it may be quite helpful for medical students on clinical rotations or residents studying for board examinations in neurology or neurosurgery.

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Critical Appraisal: This little treasure contains an abundance of information presented in a concise, user-friendly format. It should be on the shelf (or pocket) of every undergraduate, medical student, or resident studying neuroanatomy and neurophysiology.

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The Neurology of AIDS, 2nd Edition

Scope: This is designed to be an encyclopedic or comprehensive text for those involved in the clinical care or research in AIDS.

Strengths: This 800-page treatise covers basic biology and immunology, mechanisms of neurotoxicity, HIV-1 dementia encephalopathy, and clinical and pathologic features, but not particularly neuro-ophthalmologic aspects. However, it is priceless in its critical review of diagnostic options, including imaging and laboratory studies and medical therapy. Antiretroviral strategies are summarized for children and adults.

Weaknesses: Animal model systems probably have minimal interest to the clinician and are well known to researchers. Neuropsychologic, social, legal, ethical, and behavioral aspects may be of less interest to physicians but will be very helpful to staff and family members of AIDS patients.

Recommended Audience: This book would be of interest to those who deal with AIDS patients on any level. AIDS patients and their family members or significant others will welcome this comprehensive resource.

Critical Appraisal: This is a marvelous, ready reference book. The scientific reviews of disease presentations, evaluations, and treatments will appeal to patients and to caregivers of all sorts. The book is unusual in its attention to the humane aspects of dealing with the disease.

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A Compendium of Inherited Disorders and the Eye

Scope: This is the 18th monograph in a series developed by the American Academy of Ophthalmology. Edited by a renowned pediatric ophthalmologist and geneticist, it is a multiauthored textbook, with four major contributors: M. L. Garcia, I. H. Maumence, A. L. Murphree, and K. Zhang. The text is an alphabetic compendium of inherited eye diseases, with each disease usually given one or two pages. Information comes largely from the Online Mendelian Inheritance in Man (OMIM), including number, inheritance, gene/gene map, epidemiology, clinical findings, ocular findings, therapeutic aspects, references, and resources. Many subjects are augmented by clinical and ocular photographs. The compendium is preceded by a 32 page introduction to the fundamentals of genetics, including inheritance, identification of disease genes, and molecular genetics.

Strengths: Although much of this information is available on-line, this written compendium has distinct advantages over electronic resources. It is written by ophthalmologists for ophthalmologists. The introduction is a concise and informative guide. It will enable any physician to learn the language of geneticists and allow comprehension of the latest genetic advances.

The emphasis in each brief entry is on the ophthalmic aspects of the disease and therapeutic considerations. It is advantageous to be able to pick a book off the shelf, flip through the pages in alphabetical order, and quickly get a synopsis of what is known about a particular disease. Also, electronic databases do not always have quality control and consistency of format. Although written by scores of authors, the contributors and editor have conferred a degree of consistency and quality control on the work that electronic resources sometimes lack. Each topic contains lists of sources where patients and physicians can obtain additional information about a particular disease. Support groups for patients, parents, and families are listed as well as centers where physicians may obtain genetic testing. Finally, the clinical and ocular photographs serve to illustrate the clinical and ophthalmic findings associated with many diseases.

Weaknesses: Some physicians may have become accustomed to using electronic sources that are free and can be updated more quickly. The field of genetics is changing so rapidly that textbooks such as this may quickly become outdated as genes are identified and their physiologic functions elucidated. In addition, electronic resources can offer links to references and resources with a mouse click.

Recommended Audience: Anyone who deals with genetically determined disorders affecting the eye and visual system will benefit from this book.

Critical Appraisal: For the ophthalmic geneticist and bench researcher, electronic databases may be more
helpful. However, even this audience can benefit from the clinical descriptions and photographs that bring to life a disease beyond DNA mutations. For the clinician who encounters these diseases, a text such as this is probably a better resource. And for the physician who just wants to become up-to-date on the inner language of genetics, the introduction section is immensely helpful.

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Handbook of Neurosurgery, 6th Edition

Scope: This 1,000-page, single-authored paperback, now in its sixth edition, is among the most popular sources of practical information for the neurosurgical house officer. Why would a neuro-ophthalmologist want to read it? Because, like the storied medicine handbook known as the "Washington Manual," this hefty little book contains information you want but cannot find in standard textbooks or journal articles. It provides the accepted guidelines for how neurosurgeons manage head trauma, trigeminal neuralgia, increased intracranial pressure, brain tumors, and brain aneurysms. It deals with issues normally handled by neurologists, such as the dizzy patient and Parkinson disease. It even opines on neuro-ophthalmic problems such as optic neuritis and ocular motor cranial nerve palsies—sensibly and very concisely.

Strengths: There cannot be a single paperback out there with more practical information on the skull, the brain, the spinal cord, and the nerves. Having passed through six editions, it has been pared to the essentials. The author has a brilliant sense of how to wrap a topic and make you remember the key issues. The tables and schematic drawings (mostly of anatomy) are simple and easy to grasp. Even the references are of prime value.

Weaknesses: You cannot expect a single author to be good at everything. Some topics are oversimplified. But this is a handbook, not a reference text.

Recommended Audience: This book would be useful for any physician who takes care of patients with neurosurgical issues.

Critical Appraisal: If you care about the underpinnings of neurosurgical practice and are curious about what the house officers are carrying in their coats, read this book. After all, neurosurgery is a craft, and a craft is best explained in a handbook, not a textbook. After six editions, this one has become a formidable resource.

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In beneficent warm and sunny late fall weather, 375 neuro-ophthalmologists enthusiastically gathered in Tokyo for the 16th International Neuro-Ophthalmology Society (INOS) meeting, 3rd Asian Neuro-Ophthalmology Society (ASNOS) Meeting, and 44th Japanese Neuro-Ophthalmology (JNOS) Meeting from November 29 to December 2, 2006. The first three days belonged to INOS and the fourth to ASNOS and JNOS. The venue was the famous Zojoji Temple, the burial grounds of the Tokugawa shoguns, a tranquil medieval refuge in the center of a furiously bustling modern Tokyo.

Adjacent to this magnificent Buddhist shrine, where incense burned and Buddhist monks quietly scurried about their chores, the conference chambers brought together attendees from 31 countries, including 214 from Japan, 64 from other Asian countries, 54 from Europe, 34 from the Americas, 4 from the Middle East, and 2 from Africa.

The Japanese hosting committee put in an astounding organizing effort. Masato Wakakura, MD (Tokyo) was the lead, and he was amply supported by Waki Fujie, MD (Tokyo), Satoshi Ishikawa (Tokyo), Kazuo Mukuno, MD (Yokohama), Osamu Mimura, MD (Nishinomiya), Motohiro Kiyosawa, MD (Tokyo), Satoshi Kashii, MD (Osaka), Kenji Kitahara, MD (Tokyo), Akio Tabuchi, MD (Kurashiki), Shotai Kobayashi (Matsue), Takagi Mineo (Niigata), Takehiko Bando, MD (Niigata), Hideki Chuman, MD (Miyazaki), Takashi Fujikado, MD (Osaka), Masato Hashimoto, MD (Sapporo), Hiroshi Ishikawa, MD (Tokyo), Yuzo Nakao, MD (Osaka), Kazuo Nakatsuka, MD (Oita), Yoshitaka Yamagata, MD (Nishinomiya), Shuichi Yamamoto, MD (Chiba), Hiroshi Yoshida, MD (Tokyo), Takeshi Yoshitomi, MD (Akita), Haruki Abe (Niigata), Hitoshi Ishikawa (Sagamihara), Ohde Hisao (Tokyo), Akihiro Ohira (Tokyo), Ko Sahara (Aichi), Keigo Shikishima (Tokyo), Takeshi Utsumi (Takatsuki), and Hiroko Yamamoto (Nagoya).

The INOS program extended over 3 full days and included more than 60 platform presentations and 226 posters. Major thanks are due to symposium organizers Neil Miller, MD (Baltimore, MD), Randy Kardon, MD (Iowa City, IA), May-Yung Zen, MD (Tokyo), David Zee...
David Zee, MD (Baltimore, MD) proposes a novel explanation of saccadic intrusions.

Particularly notable were presentations of current evidence for the efficacy of thrombolysis in central retinal artery occlusion, results of intensive study of a Brazilian cohort of Leber hereditary optic neuropathy, experimental evidence for a retinocollicular melanopsin pathway affecting the pupillary reflex, a recapitulation of the work of Kenji Ohtsuka on the physiology of the near reflex, a creative hypothesis for the pathophysiology of saccadic intrusions, investigation of a giant registry of Japanese
Gagaku, sacred Japanese music and dance dating from more than 1,400 years ago, performed by the Buddhist monks of Zojoji Temple.

Before the Walsh in Asia program began, Jeff Burde accepted a recognition award on behalf of his father Ronald Burde, MD, for Dr. Burde’s long dedication to teaching neuro-ophthalmology in Japan. The award acknowledged the Ronald Burde Study Group, founded over a decade ago in Japan, under whose auspices the Walsh in Asia program will be sponsored in the future.

To supplement the academic activities, the organizers had prepared a magnificent social program including sessions on Japanese flower arrangements, holiday decorations, wedding dress, hina dolls, origami, and tea ceremonies. The Buddhist monks from Zojoji Temple gave a concert of gagaku, Japanese sacred music and dance.
The requisite group photo of meeting attendees. There were 375.

Dusk over the meeting site, with Zojoji Temple (medieval Japan) in the foreground and Tokyo Tower (modern Japan) in the background.

dating from over 1,400 years ago. There was a whistling concert in the temple itself, rides in jinrikisha, the human-powered transport called “rickshaw” in English, a performance of Noh, traditional Japanese theater, and a tour of the mausoleum of the Tokugawa shoguns. The box lunches, a Japanese specialty, were always a surprise and an adventure.

By the time the meeting had drawn to a close, it was clear that a new standard had been set for the organizers of the next (17th) INOS meeting, which will be held at the Silverado Resort in Napa, California, on June 7–12, 2008. The next (45th) annual JNOS meeting will be held in Osaka, Japan, on November 30–December 1, 2007, and the next (4th) ASNOS meeting will be held in Taipei, Taiwan, on May 16–18, 2008.

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Retinal Migraine

In this issue of the *Journal*, I am a coauthor of the manuscript on retinal migraine by Hill et al (1). I was somewhat responsible for “retinal migraine” remaining in the second edition of the International Headache Society (IHS) Classification (2) and will relate how this transpired.

Dr. Jes Olesen, Professor and Chairman of Neurology at the University of Copenhagen, was chair of the first Headache Classification Subcommittee, the results of which were published in 1988 (3). At the Migraine Trust International Symposium in London in 1994, I presented a paper on “The Eye and Headache” that included a brief mention of retinal migraine. Olesen told me that he doubted the existence of retinal migraine, because most patients did not have IHS-defined migraine. I replied that I had seen at least one bona fide case when I was at the University of Miami (1968–1980), and would try to locate my records.

I wrote Olesen on September 21, 1994, as follows:

Dear Jes:

Since I always assumed that retinal migraine existed, I didn’t keep records of the patients I had seen. However, in going over my Miami files, I came across two patients whose records are enclosed.

1. Case 1 had repetitive unocular events and migraine headaches but only one episode of migraine associated with a monocular visual aura. The two follow-up notes indicate apparent resolution by propanolol.

2. Case 2, the wife of an ophthalmologist, is an absolutely unequivocal case as indicated in my enclosed 5-11-72 office note. Since taking the propanolol, she has stopped having episodes.

I conclude that retinal (anterior visual) migraine exists but is extremely rare (if coexistent migraine headaches are required with more than a single episode).

Sincerely yours,
Bob

Case 1 was not a “definite retinal migraine,” but Case 2 seemed to be. Her relevant history, obtained on May 11, 1973, is as follows. She was the 26-year-old wife of a local ophthalmologist who had had her first migraine in 1967 at age 20. It consisted of a pulsating left temporal headache with nausea and vomiting. She was then asymptomatic until 1970, when she developed sudden visual loss in the left eye. She happened to be in the vicinity of the Bascom Palmer Eye Institute of the University of Miami School of Medicine and saw one of the neuro-ophthalmologists who confirmed a central scotoma in the left eye. An hour later, she developed a pulsating left temporal headache that lasted about 12 hours. The scotoma cleared about 3 hours after the onset of the headache. Subsequently, she had several left-sided headaches preceded by the left eye visual loss, the last occurring 3 weeks before her visit with me. I prescribed propanolol, and her episodes abated, at least until 1980, when I left Miami for Cleveland and lost contact with her.

Olesen agreed that Case 2 was an “indisputable” example of retinal migraine. He later chaired the Second IHS Headache Classification Subcommittee, the results of which were published in 2004 (2), in which “retinal migraine” remained included.

I have not seen a case of definite retinal migraine since leaving Miami in 1980. Several years ago, I asked four neuro-ophthalmologists in northeast Ohio how many patients they had seen with “IHS-defined retinal migraine,” and the response was zero.

Monocular visual loss may be associated with migraine, but as indicated by Hill et al (1), it is exceptionally rare.

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REFERENCES


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Fluctuating Ptosis, Diplopia, and Normal Pupils With Intracavernous Aneurysm

A 67-year-old woman was referred to the department of ophthalmology of our institution with a 4 month history of headache, intermittent vertical diplopia, and fluctuating left upper lid ptosis, which was often worse in the afternoon (Fig. 1). She had a history of systemic hypertension.

Best-corrected visual acuity was 20/60 in each eye. Ocular motility examination in the right eye was normal. In the left eye, there was a very variable and apparently
fatigable ptosis, with palpebral fissures measuring 6 mm on the left and 10 mm on the right. Abduction, adduction, and infraction were normal in the left eye, but supraduction was reduced to approximately one-third of the normal range. There were no pupillary abnormalities. The rest of the ophthalmologic examination was unremarkable, as was the neurologic examination.

Three days later, anisocoria was first noted, with the right pupil measuring 4 mm in dim illumination and reacting briskly to light and the left pupil measuring 6.5 mm and reacting sluggishly to light. There was no relative afferent pupillary defect.

MRI and magnetic resonance angiography (MRA) showed a 22.5 mm diameter saccular aneurysm arising from the cavernous and supraclinoid segment of the left internal carotid artery (Fig. 2). The patient was offered coiling but declined.

Aneurysmal third cranial nerve palsy is usually caused by aneurysms that arise from the junction of the internal carotid artery and posterior communicating artery (89%) but can be caused from aneurysms located in the intracavernous internal carotid artery (6.2%), as found in our patient, or in the basilar artery (3.4%), posterior cerebral artery, or superior cerebellar artery (1,2).

In patients with aneurysmal third cranial nerve palsy, pupillary reactions are usually affected first, followed by ptosis, and finally extraocular muscle paralysis affecting the medial, superior, and inferior rectus and oblique muscles (2,3). Ptosis caused by aneurysmal third cranial nerve palsy is usually not variable (1). The marked fluctuation in ptosis seen in our patient has been reported only rarely (4). It has been attributed to intermittent hyperfunction of the muscles supplied by the third cranial nerve. Coexisting inappropriate neural discharge with blockage is the presumed mechanism (4).

The presence of fluctuating unilateral ptosis in an elderly patient with minimal extraocular muscle dysfunction and pupil-sparing does not rule out intracavernous aneurysmal compression.

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REFERENCES
Amiodarone and Ischemic Optic Neuropathy

Since the original articles (1,2) about the occurrence of anterior ischemic optic neuropathy (AION) during administration of amiodarone were published in 1987, many articles and case reports of a possible causal relationship between the neuropathy and amiodarone have emerged. I have closely followed these articles and case reports. They cover about 100 cases to date and probably underreport the actual incidence. As a coauthor of the initial study (2), I have been concerned that the higher incidence of AION in amiodarone users than in an age-matched group of nonusers, although statistically significant ($P = 0.001$) in that report, could have been due to chance alone, because most of the amiodarone users were likely to have had substantially more vascular disease.

Indeed, the purpose of the initial study was to determine the efficacy of amiodarone in saving the lives of patients with serious cardiac arrhythmias. Despite amiodarone use, 26% of the 447 patients in this study group died by the time the study was published. Because of the substantial morbidity and mortality, it would be ethically impossible to repeat such a study in a similar group of patients using a control group of untreated patients. Many of these untreated patients would die of cardiac arrhythmias. The lifesaving effect of amiodarone in serious cardiac arrhythmias is thus far unsurpassed (3), although in recent years, implanted cardiac pacemakers have been used more often, sometimes with amiodarone supplementation.

To ascribe a cause-and-effect relationship to a drug and a presumed side effect, researchers would expect to see a substantial increase in the incidence of the side effect in the treated group compared with a similar group of untreated patients or patients treated with a different agent or device. A huge increase in the incidence of AION has not been seen in amiodarone users, despite the fact that thousands of patients have taken the drug. Thus, the occurrence of AION in patients taking amiodarone might be by chance alone.

None of the literature describing the so-called entity of amiodarone optic neuropathy, including the article that I cowrote (2), provides a scientific basis for proving a cause-and-effect relationship by means of a prospective controlled study. Look at the design of such a study, with a few assumptions. The actual incidence of optic neuropathy in patients taking amiodarone is not known. If researchers use the widely quoted figure of 1.79%, which was determined in patients who had preexisting cardiac dysrhythmias (2), a study would have to have a substantial number of patients in both a treated group (about 900) and an untreated group (well over 1,000). Also, patients would need to be observed prospectively for a sufficiently long period to determine the incidence of clinically significant side effects with only 80% power.

Given these numbers, as well as the better-known rates of side effects of amiodarone on other systems, investigators would expect to see these side effects, some of which are serious and clinically significant, develop in a certain percentage of the treated patients. Among amiodarone users, 2.5% would have peripheral neuropathy, 39% ataxia, 37% staggering, 4%–25% liver function abnormalities, and 2%–17% pulmonary infiltrates (some of which may be lethal). During the study, about 26% of the treated group might die of cardiac disease.

Consider the control group. To be representative, the control group would have to have the same characteristics as the treatment group, including clinically significant cardiac dysrhythmias, many of which are life-threatening. If the patients need alleviation of their dysrhythmias, a technique or agent other than amiodarone would have to be used. However, that use would make the control group different from the treatment group. Investigators might expect that in the untreated group, a higher percentage of patients would die of cardiac disease—perhaps as many as 50%.

Getting approval for such a “high-risk” study by an institutional review board would be highly unlikely because the study would be unethical. This study design would be the equivalent of studying patients who have insulin-dependent diabetes by treating half the patients with insulin and not giving insulin to the other half as a way to measure a difference in disease complications.

Many ophthalmologists have seen patients who present with bilateral simultaneous AION. They have also seen patients in whom visual loss has occurred in one eye because of acute AION and the other eye is already pale, indicating bilateral disease that is as yet unknown to the patient. If patients with AION are evaluated soon after one eye has been affected, some optic disc swelling may be seen eventually and before the onset of visual loss in the fellow eye (4). A recent Israeli prospective study of 23 patients who had optic disc edema without initial visual loss (5) points out that optic disc edema can be present for some time in the absence of visual loss. In 64% of this study group, the edema resolved without development of AION and in a mean of 15.5 weeks. Although the four patients in the small group taking amiodarone did not have AION, this
sample size is too small to be meaningful. The findings of
the study illustrate how difficult it is to delineate a clinical
difference between “typical” AION and AION associated
with amiodarone use.

Because some clinical features in patients who have
AION associated with amiodarone use have differed from
those in patients with spontaneous AION (6,7)—a higher
incidence of simultaneous bilateral AION, a less severe
effect on vision, and a higher incidence in men—several
researchers have concluded that there must be a cause-and-
effect relationship. I agree that this is possible, but the proof
is lacking.

Until a study can be designed that poses no additional
risk to the patients being studied and given that both
a control group and a group of patients with cardiac disease
would need to be studied, there is no justification to assert
that a cause-and-effect relationship exists between amio­
darone and AION. Nonetheless, it is prudent to advise the
treating cardiologist and the patient of possible adverse
effects on vision with amiodarone use. If an amiodarone
user experiences a change in vision, that patient should seek
immediate attention from an opthalmologist. If disc swel­
lings or visual loss or both occur, cessation of amiodarone
treatment should be seriously considered and a switch to
a different agent or a pacemaker should be made. Even so,
the consequences of stopping an effective antiarrhythmic
treatment such as amiodarone should be considered on
a case-by-case basis, taking into account the best interests
of the patient.

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REFERENCES
Upcoming Meetings

April 11–April 15, 2007
American Association of Pediatric Ophthalmology & Strabismus (AAPOS) Annual Meeting
Seattle, WA
http://www.aapos.org/
Contact: aapos@aao.org

April 14–April 19, 2007
75th American Association of Neurological Surgeons (AANS) Annual Meeting
Washington, DC
Contact: info@aans.org

April 28–May 5, 2007
59th Annual Meeting of the American Academy of Neurology (AAN)
Boston, MA
http://aan.aan.com/
Contact: membership@aan.com

May 6–May 8, 2007
Society of Neurological Surgeons Annual Meeting
San Francisco, CA
http://www.societyns.org/meeting/index.html

May 6–May 10, 2007
Association for Research in Vision and Ophthalmology (ARVO)
Ft. Lauderdale, FL
Contact: arvo@arvo.org

May 26–May 29, 2007
European Neuro-Ophthalmology Society (EUNOS)
Istanbul, Turkey
http://www.eunos2007.org/
Contact: info@eunos2007.org

May 29–June 1, 2007
European Stroke Conference
Glasgow, UK
http://www.eurostroke.org/
Contact: haunerici@eurostroke.eu

May 31–June 3, 2007
XXVII Pan-American Congress of Ophthalmology (PAAO)
Cancun, Mexico
http://www.paaocancun.org.mx/eng/index.htm
Contact: pao2007@servimed.com.mx

June 7–June 10, 2007
49th Annual Scientific Meeting of the American Headache Society
Chicago, IL
http://www.ahsnet.org
Contact: ahsmtgse@talley.com

June 9–June 12, 2007
16th Congress of the European Society of Ophthalmology (Socites Ophthalmologica Europaea)
Vienna, Austria
http://www.soe2007.org/
Contact: secretariat@soevision.org

June 9–June 15, 2007
45th Annual Meeting of the American Society of Neuroradiology (ASNR)
Chicago, IL
http://www.asnr.org/2006/
Contact: ltannehill@asnr.org

June 16–June 20, 2007
17th Meeting of the European Neurological Society
Rhodes, Greece
http://www.akm.ch/ens2007/
Contact: ENS2007@frei.ch, ensinfo@akm.ch

June 19–June 22, 2007
Canadian Congress of Neurological Sciences Annual Meeting
Edmonton, Alberta, Canada
http://www.ccns.org/ccns_information/events/annual_meeting/general_info.html
Contact: web@ccns.org

June 20–June 23, 2007
Canadian Ophthalmological Society
Montreal, Quebec, Canada
Contact: cos@eyesite.ca

June 28–July 1, 2007
13th Congress of the International Headache Society
Stockholm, Sweden
http://www.ihsc2007.org/
Contact: ihsc2007@stocon.se

July 12–July 17, 2007
IBRO World Congress of Neuroscience
Melbourne, Australia
http://www.ibro2007.org/
Contact: ibro2007@sallyjayconferences.com.au
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