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Incidental Asymptomatic Orbital Calcifications

Jennifer L. Murray, M.D., L. Anne Hayman, M.D., Rosa A. Tang, M.D., and Jade S. Schiffman, M.D.

Abstract:
Objective: To use modern computed tomography (CT) imaging to quantify the incidence of asymptomatic incidental orbital calcifications and describe their histological features.

Materials and Methods: One hundred orbital CT scans were reviewed. In addition, patients who had orbital calcification(s) detected on a brain CT scan were examined by the ophthalmology service.

Results: Of the orbital CT scans, 2% had bilateral drusen of the optic nerve head, 3% had calcified scleral plaques anterior to the medial or lateral rectus muscles, and 3% had bilateral ossification of the trochlear apparatus. Routine brain CT scans detected asymptomatic calcifications of the sclera and dura surrounding the proximal optic nerves.

Conclusion: Incidental asymptomatic orbital calcifications are commonly encountered on modern high-resolution CT images of the brain and orbit. This article should help the clinician to confidently distinguish these densities from foreign bodies or pathological calcifications.

Key Words: Computed tomography—Orbit—Calcification—Drusen—Trochlear apparatus—Medial/lateral rectus muscle—Dura ossification—Dura mater.

The computed tomographic (CT) literature that describes orbital calcification is more than a decade old (1–4). Modern high-resolution scanners have greatly improved the sensitivity of this technique, and calcifications in asymptomatic individuals are now routinely seen. These can initiate unwarranted concern that a pathological process or foreign body is present. The purpose of this article is to provide a practical guide to the imaging features of these incidental calcium deposits. It illustrates benign calcifications in the optic nerve head, trochlear apparatus of the superior oblique muscle, the sclera, and the proximal dural sheath of the optic nerves.

MATERIALS AND METHODS

The material for this article came from two studies. The first was a retrospective orbital CT study on 100 unselected Ben Taub General Hospital patients who were examined by two authors (J.M., L.A.H.). Scans with motion artifacts were excluded from consideration. A General Electric 9800 Signa Scanner was used for all cases. Eighty-nine cases had 3-mm axial and coronal views of the orbits. All of the data were filmed in narrow (soft tissue) and wide (bone window) settings. The CT scan slices were angled to avoid dental-filling artifacts. The scans in the remaining 11 cases had only axial views of the orbit.

The incidence of calcification in the optic nerve head, sclera, and trochlear apparatus of the superior oblique muscle was noted. The sex and age of each patient was recorded. The medical charts of all cases with calcifications were reviewed for orbital or systemic pathological conditions or both. No attempt was made to determine the race of each patient because diversity is the hallmark of our patient population.

The second study was a 6-month review of brain CT scans to detect orbital calcifications. Cases in
which calcifications were seen in areas not described in the orbital study were selectively referred to the ophthalmology clinic for evaluation.

RESULTS

This retrospective orbital CT study analyzed 199 orbits in 100 patients. One patient had destruction of the right globe by a gunshot blast. The mean age was 35 years; the range was 3 to 85 years old. There were 28 female and 72 male patients in the study. Calcifications were noted in 8% of the patients. Two patients, one female and the other male, had bilateral drusen of the optic nerve head (Fig. 1). Three patients had bilateral calcifications in the trochlear apparatus of the superior oblique muscle (Fig. 2A and B). This group contained two men (30 and 48 years old) and one girl (16 years old). None of them had diabetes.

Two patients had scleral calcifications. A 65-year-old man had bilateral calcified scleral plaques anterior to the insertion of the lateral rectus muscle (Fig. 3). An 85-year-old man had a unilateral calcification of the sclera medial to the insertion of the medial rectus muscle (Fig. 4).

The review of the brain CT scans demonstrated three patients with orbital calcifications in areas not described in the first orbital survey. There were two women (43 and 48 years old) and one man (55 years old). Two cases had scleral calcifications (Figs. 5 and 6). Bilateral calcifications that appeared to be in the dural sheath surrounding the proximal optic nerve were seen in one case (Fig. 7). None of these cases had a history of trauma, in-

FIG. 1. Axial computed tomography shows bilateral calcification (arrowheads) in the substance of the optic nerve head, consistent with the diagnosis of optic nerve drusens.

FIG. 2. Coronal (A) and axial (B) computed tomography scans show calcification in the cartilaginous portion of the trochlear apparatus of the superior oblique muscle (arrowheads).

FIG. 3. Axial (A) and coronal (B) computed tomography scans show bilateral calcification in the sclera (arrowheads) just anterior to the insertions of the lateral rectus muscles, consistent with calcified scleral plaques.

Drusen of the Optic Nerve Head (Fig. 1)

On CT, drusen appears as a discrete, rounded high density confined to the optic disc surface (Fig. 1). CT scans are so sensitive that they may detect drusen when the ophthalmoscopic examination is apparently normal. Therefore, the incidence of drusen by ophthalmoscopic observation was reported as only 0.34% of the population in Denmark (3). In this CT study, it was found in 2% of the heterogeneous population of patients examined at a large county hospital.

Drusen of the optic disc was first described in
1858 (5). It is inherited as an irregular dominant trait, primarily in blond whites. It may be referred to as a "hyaline body" of the optic nerve head because it is a calcific cellular accretion of hyalinelike material. It is usually buried within the substance of the nerve head anterior to the lamina cribrosa. It is covered by axons, glia, and the vessels that supply the nerve head. It can cause a distortion in the shape of the nerve, which causes the margins of the disc to become blurred or "lumpy," making it difficult to delineate them from the surrounding retina. Thus the drusen can be confused with disc edema on ophthalmoscopic examination; therefore, a CT may be ordered to rule out a space-occupying lesion. However, B scan ultrasonography is the procedure of choice to detect buried drusen. Retinoblastomas and optic nerve gliomas are among the few lesions that may produce calcification of the posterior globe. Knowing the differences in radiologic presentation of these three entities is important in differentiating a benign from a more serious cause of pseudopapilledema (1,2). Clinically, 87% of patients with drusen may even develop arcuate visual field defects and optic disc hemorrhage (3).

Trochlear Apparatus Calcification (Fig. 2)

The trochlear apparatus of the orbit is the cartilaginous structure through which the superior oblique tendon and its sheath pass. The exact site of calcium deposition has not been determined by anatomic studies. Possibilities include the tendon of the superior oblique muscle, the synovial sheath, and the cartilage (6). In this study, high-resolution CT images clearly showed that the calcifications were in the cartilage (Fig. 2).

A recent CT study suggests that calcification in the trochlear apparatus is strongly associated with diabetes in patients younger than 40 years (6). In that study, 12% of patients (19 of 159) had calcification in the trochlea apparatus. Our study found an incidence of only 3%. This may be because none of our patients had diabetes, even though two of the three were younger than 40 years.

Scleral Plaques (Figs. 3-6)

Calcification of the sclera has been reported at sites of focal senile thinning that occur anterior to
FIG. 7. Axial (A, B) and coronal (C) computed tomography scans show calcification in the medial aspect of the dural sheath (arrowheads in A and B) surrounding the proximal optic nerves.

the tendinous insertions of the medial or lateral rectus muscles (Figs. 3–5) (7). In this study, focal calcification was also found at the insertion of the superior rectus muscle (Fig. 5). These areas are commonly seen by the ophthalmologist and were identified in 3% of the orbital CT studies reviewed for this article.

Scleral thinning and calcification may be caused by hyaline degeneration or may be secondary to the mechanical stresses created by contraction of the rectus muscles. The frequent occurrence of plaques in the elderly supports this concept. In this study, the youngest patient with scleral calcifications was 48 years of age. If unilateral scleral calcification could be found in a patient with congenital contralateral palsy of a rectus muscle, it would supply the evidence needed to substantiate this mechanistic theory.

Asymptomatic calcification of the sclera at sites other than muscle attachments can rarely occur (Fig. 6). Focal calcifications have been noted in the posterior sclera of patients with hyperparathyroidism, vitamin D intoxication, and milk-alkali syndrome. In these cases, the scleral calcifications tend to be more diffuse and not so localized as those seen at the tendinous insertions (1).

Dural Ossification (Fig. 7)

The dura mater is composed of fibrous tissue and elastic fibers. Its inner surface consists of mesothelial cells. Under pathological situations, they can act as fibroblasts. For unknown reasons, these cells may undergo metaplastic change and form bone. These ossified plaques may be found in the dura of the flax, tentorium, and calvaria of 10% of normal individuals. However, this incidence may be increased in patients with endocrine disorders (8). In our study, we found a case of bilateral symmetric ossification in the dural sheath of the optic nerve (Fig. 7). This is easily distinguished from the unilateral calcification(s) seen in symptomatic patients with meningiomas of the optic nerve sheath or optic nerve glioma. To the best of our knowledge, incidental calcification of the dura of the optic nerve sheath has not been reported previously in the literature.

CONCLUSION

A thorough knowledge of the location of physiologic orbital calcifications will prevent confusion when orbital CT scans are examined for the possibility of a foreign body. In addition, familiarity with these densities allows the imaging clinician to confidently distinguish asymptomatic incidental orbital calcifications from pathological conditions.

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REFERENCES


Recovery from Ocular Ischemic Syndrome After Treatment with Verapamil

Jacqueline M. S. Winterkorn, Ph.D., M.D., and Richard L. Beckman, M.D.

Vasospasm has been implicated as a cause of amaurosis fugax, which can be controlled by administration of the calcium channel blockers nifedipine or verapamil. However, vasospasm has not previously been thought to be involved in chronic ocular ischemia. We report a patient with ocular ischemic syndrome, which may have had vasospasm as a contributing cause, since the patient also developed amaurosis fugax despite daily aspirin therapy. An 80-year-old man with chronic open-angle glaucoma developed chronic ocular ischemia characterized by progressively decreased visual acuity, pain, rubeosis, and hypotony, as well as transient visual dimming. Medical evaluation revealed no evidence of carotid stenosis, thromboembolism, or vasculitis as the cause of ocular ischemia. When the calcium channel blocker verapamil was administered, the episodes of transient visual dimming ceased immediately. In addition, soon thereafter, visual acuity improved, the rubeosis partially regressed, and the hypotony reversed. This case indicates that the calcium channel blocker verapamil may be effective in treating cases of ocular ischemic syndrome, when vasospasm is a contributing cause.

Ocular ischemic syndrome is a condition in which hypoperfusion of the globe leads to acute and chronic defects in ocular tissues. Decreasing vision is usually accompanied by ocular pain. Other signs of ischemia in the eye include corneal clouding, uveitis, and anterior and posterior segment neovascularization. Intraocular pressure frequently is low, reflecting insufficient perfusion of the ciliary body. The most common causes of ocular ischemic syndrome include stenosis, thromboembolism, and vasculitis of the carotid artery or its branch to the eye, the ophthalmic artery. Vasospasm, which underlies some cases of amaurosis fugax or transient visual loss (1-3), has not previously been implicated as a contributing cause of chronic ocular ischemic syndrome.

We describe a patient with a history of chronic open-angle glaucoma, in whom ocular ischemic syndrome was diagnosed when he developed progressive visual loss and ocular pain and was found to have rubeosis and hypotony. The patient experienced superimposed episodes of transient visual dimming. The absence of a fixed vascular lesion and the recurrence of amaurosis fugax suggested a vasospastic component (1,2), and the calcium channel blocker verapamil was started. Not only did the episodes of transient visual dimming cease, but soon thereafter the visual acuity improved, the rubeosis partially regressed, and the intraocular pressure returned to elevated levels. These signs indicated successful medical treatment of ocular ischemic syndrome.

CASE REPORT

An 80-year-old man with mild hypertension had undergone four surgical procedures for pseudoexfoliative glaucoma in the left eye. Four years prior to this evaluation, combined cataract extraction
and trabeculectomy were performed on his left eye. The trabeculectomy failed, and the intraocular pressure remained elevated. Two years later, the patient underwent a second trabeculectomy in his left eye at another site, which also failed. A few months later, a revision of the trabeculectomy was attempted, using peribulbar injections of 5-fluorouracil (5FU). This procedure also failed to lower intraocular pressure. Finally, a year later, the patient received an erbium-YAG laser sclerostomy, but subsequently still required pressure-lowering medication, including systemic Diamox and topical pilocarpine and Timoptic. The intraocular pressure in the left eye remained between 22 and 25.

Eight months following his last surgical procedure for glaucoma, the patient reported an episode of amaurosis fugax in the left eye with visual loss lasting 10 min. Medical evaluation, including carotid duplex scanning and echocardiography, revealed no structural abnormality in the heart or carotid vasculature, and the patient was treated with daily aspirin 325 mg. A month later, the patient complained of decreasing vision and an ache in his left eye. Visual acuity in the left eye, which had been 20/25, was now 20/100. Slit-lamp examination of the left anterior chamber revealed mild iritis. Iris neovascularization was evident, continuing into the anterior chamber angle, but without angle closure. Retinal neovascularization was not seen on funduscopy or demonstrated on fluorescein angiography, although the fluorescein angiogram of the left eye did demonstrate delayed filling in the arterial phase. The right eye continued to have a normal examination with 20/20 visual acuity, full visual field, unremarkable slit-lamp examination, and intraocular pressure of 12 mm Hg without medication. In the left eye, intraocular pressure was down to 17 mm Hg.

Further medical workup did not reveal a cause for the left ocular ischemic syndrome. Blood tests were normal, including those for hypercoagulability (complete blood count, Westergren sedimentation rate, blood chemistry, anti-nuclear antibody, anti-cardiolipin antibody, protein C, protein S, factor VIII, anti-phosphotidylcholine and -serine). Neither carotid stenosis nor significant plaque were demonstrated on magnetic resonance imaging or magnetic resonance angiography. Bilateral temporal artery biopsies were negative. The iritis did not resolve with topical steroid therapy, and the intraocular pressure progressively fell despite decreasing glaucoma medication, until it stabilized at 12 mm Hg after all medications for glaucoma had been discontinued. The patient continued to take 350 mg of aspirin daily, and diltiazem for hypertension. His condition did not improve over the next four months: examination of the left eye continued to show visual acuity of 20/100, and intraocular pressure decreased to 12 mm Hg off all glaucoma medication. The patient then reported several episodes of amaurosis fugax in the left eye, consisting of darkening of his vision over ~3 min to total visual blackout and followed by resolution to baseline. No visual disturbance occurred in the right eye. In a patient with neither carotid stenosis nor an embolic source, these recurrent episodes of amaurosis fugax despite daily aspirin therapy suggested the diagnosis of vasospasm in the circulation of the anterior visual pathways (1). After discussion with the patient's internist, the calcium channel blocker verapamil, previously demonstrated to be clinically beneficial in patients with amaurosis fugax of vasospastic etiology (2), was substituted for diltiazem. Verapamil was prescribed in slow-release form 120 mg twice daily. No significant change was seen in blood pressure control on periodic office measurements or on an ambulatory 24-h monitoring. No further episodes of amaurosis fugax occurred, and the pain in the left eye resolved. On examination two weeks later, the patient reported improved vision in his left eye, and examination recorded visual acuity of 20/50 + OS. Examinations during the succeeding weeks found regression of the rubeosis. The intraocular pressure rose again to the low 20s and required reintroduction of antiglaucoma therapy.

The patient's improved condition has been stable now for two years.

**DISCUSSION**

This case provides support for the hypothesis that vasospasm in the ocular circulation contributes to visual loss and that calcium channel blockers may be effective in treating ocular conditions caused by vasospasm. Prior reports (1,2) have indicated that vasospasm may precipitate amaurosis fugax in some patients. Patients with amaurosis fugax whose medical evaluation did not demonstrate an embolic source and whose attacks did not resolve with antiplatelet or anticoagulating agents experienced cessation of amaurotic attacks immediately upon treatment with a therapeutic dose of nifedipine or verapamil. Furthermore, when the medication was discontinued, the symptom recurred until the medication was restarted.

The patient described here, like the patients previously reported with vasospastic amaurosis fugax, had no further attacks of transient visual loss after starting therapy with verapamil. In addi-
tion, soon after starting verapamil, this patient experienced reversal or relief of chronic symptoms and signs of ocular ischemia, including improvement in visual acuity, resolution of iritis, regression of rubeosis, and elevation of intraocular pressure by 10 mm Hg, all suggesting increased ocular perfusion.

In this patient, the calcium channel blocker verapamil was apparently successful at reversing ocular ischemia, even though another calcium channel blocker prescribed for treatment of hypertension, diltiazem, had not proven protective. This observation is consistent with the pharmacology of calcium channel blockers (3), a widely diverse family of agents differing in therapeutic mechanism and efficacy at different sites of action. The effects of calcium channel blockers have been ascribed to their capacity to reduce toxic levels of intracellular calcium, stabilize membranes, and increase perfusion by vasodilating and to their interaction with intracellular messengers, cyclic nucleotides, and neurotransmitters. At least two types and four subtypes of biochemically unique calcium channels have been identified in several tissues, acting differently to pump calcium out of cells in the event of tissue destruction. Calcium channel blockers differ in their ability to recognize and to modulate these distinct calcium channels in various tissues. But while the presence of extracellular calcium and its influx into cells during anoxia are critical in producing neuronal damage, that influx in vitro does not seem to take place through dedicated calcium channels, but rather through a sodium-calcium ion exchanger, in part explaining why calcium channel blockers have not provided effective protection against glaucoma and ischemic optic neuropathies. In addition, they also differ importantly in the degree to which they influence other neurotransmitter systems, for example, by alpha stimulation, beta blocking, and postsynaptic modulation (3-6). Such differences may underlie the contrary and controversial results obtained using different calcium channel blockers in studies attempting to improve ocular blood flow in chronic open-angle glaucoma and low-tension glaucoma (7,8). Whereas nifedipine and verapamil have been reported to decrease intraocular pressure, leading to stabilization or improvement of visual field in chronic open-angle glaucoma (9), trials with other calcium channel blockers have been inconclusive. So far, diltiazem has not proven effective in treating ocular conditions.

Therefore, possible reasons for the superior response of this patient's ocular problems to verapamil compared with diltiazem, while at the same time achieving comparable blood pressure control, include the greater influence of verapamil on ocular circulation and the relative cardioselectivity of diltiazem, the effect of verapamil on both alpha-1 and alpha-2 adrenergic receptors, and the greater potency of verapamil, resulting in its acting as a stronger vasodilator at much lower doses than diltiazem.

This case suggests that vasospasm may play a role in ocular conditions caused by ischemia and that calcium channel blockers may provide effective therapy for such conditions. The clinical success of calcium channel blockers in the treatment of diseases involving ocular ischemia will depend upon the wise or fortunate choice among agents to be tested in clinical trials. This choice should be based upon understanding of biochemical interaction with a variety of receptors in ocular structures, some of which have yet to be defined.

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Rapid Growth of an Intracranial Aneurysm Causing Apparent Retrobulbar Optic Neuritis

Neil R. Miller, M.D., Peter J. Savino, M.D., and Timothy Schneider, M.D.

We describe a 31-year-old man who developed sudden painful loss of vision in the right eye and was found to have a retrobulbar optic neuropathy. Magnetic resonance (MR) imaging gave normal results, and a diagnosis of retrobulbar optic neuritis was made. The patient was treated with oral prednisone, but he continued to lose vision in the right eye and then began to lose vision in the left eye. Repeat MR imaging performed eight weeks after the initial study showed a giant intracranial aneurysm compressing the right and left optic nerves. Cerebral angiography revealed that the aneurysm arose from the origin of the right ophthalmic artery. Treatment of the aneurysm by a trapping procedure resulted in improvement in vision in the left eye but no change in vision in the right eye. This report emphasizes the difficulty in imaging intracranial aneurysms of various sizes, the rapidity with which intracranial aneurysms can enlarge, and the importance of continued follow-up examinations in patients thought to have idiopathic optic neuritis.

Key Words: Optic neuritis—Aneurysm—Acute optic neuropathy—Magnetic resonance imaging.

A 31-year-old man presented to the Neuro-Ophthalmology Service of the Wills Eye Hospital because of a two-week history of headache, blurred vision in the right eye, and pain in the base of the neck, radiating into the right eye and temple. Neuro-opthalmologic examination at this time revealed visual acuity of counting fingers at 6 ft OD and 20/20 OS. Color vision testing using Hardy-Rand-Ritter (HRR) pseudoisochromatic plates was 8/15 OD and 14/15 OS. There was a marked right relative afferent pupillary defect, and the right visual field showed a superior altitudinal defect (Fig. 1). Ophthalmoscopy revealed normal appearing optic discs.
FIG. 1. Results of kinetic perimetry at presentation. Visual acuity was counting fingers at 6 ft OD and 20/20 OS. A: There is complete loss of the visual field of the right eye. The defect includes the central 5–10°, accounting for the decreased visual acuity. B: The visual field of the left eye is full.
The patient was thought to have optic neuritis and was enrolled in the Optic Neuritis Treatment Trial (ONTT), a controlled clinical trial supported by the National Eye Institute of the National Institutes of Health (1,3). As part of the study, he underwent MR imaging of the brain and orbits. The study was of excellent quality and showed no abnormalities. Specifically, no mass was detected in the region of the intracranial portion of the right optic nerve (Fig. 2). The patient was randomized to the oral arm of the trial, which consisted of treatment with either placebo or prednisone at a dosage of 1 mg/kg/day. Over the next 10 days, the patient experienced some reduction in pain but no improvement in vision. Treatment was continued for two weeks and then stopped, as mandated by the ONTT protocol (3). After stopping the oral medication, the patient developed worsening pain. Visual acuity in the right eye became further reduced, and vision in the left eye began to decrease. Repeat MR imaging was performed two months after the onset of visual loss and now revealed a 25 x 18 x 15-mm mass, consistent with a giant and substantially clotted aneurysm, in the suprasellar and right paracavernous regions (Fig. 3). A cerebral angiogram confirmed that the lesion was an aneurysm, and the patient was transferred to the John Hopkins Hospital.

On examination in the Neuro-Ophthalmology Unit of the Johns Hopkins Hospital, the patient had visual acuity of no light perception OD and 20/30 OS. He could identify only eight and one half of ten HRR plates slowly with the left eye, and visual field testing of the left eye using kinetic perimetry disclosed an incomplete temporal hemianopia that was denser superiorly than inferiorly (Fig. 4). The right pupil was nonreactive to direct light but did react consensually. The left pupil was briskly reactive to light and near stimulation. There was a marked relative right afferent pupillary defect. Extraocular movements were full, and the eyes were straight by Hirschberg measurement. Corneal and facial sensation were normal and symmetric bilaterally. Ophthalmoscopy revealed pallor of the right optic disc. The rest of the right ocular fundus appeared normal. The left optic disc, macula, and vessels appeared normal.

The patient underwent a repeat four-vessel cerebral angiogram that confirmed the presence of a giant, mostly clotted, aneurysm arising from the right internal carotid artery at the origin of the ophthalmic artery (Fig. 5). Shortly thereafter, he underwent a right temporal craniotomy, at which time the aneurysm was found to have a broad neck that prevented placement of an aneurysm clip across it. Accordingly, the right internal carotid artery was ligated in the neck, and a clip was placed on the suprachoroidal portion of the artery, distal to the origin of the ophthalmic artery.

Postoperatively, the patient noted immediate improvement in vision in the left eye but no change in vision in the right eye. Neuroophthalmologic examination three days after surgery revealed no light perception in the right eye; however, visual acuity in the left eye was 20/25, and the patient was now able to identify all ten of the HRR plates correctly. Visual field testing of the left eye using kinetic perimetry now showed only a relative superotemporal defect (Fig. 6). The rest of the examination was unchanged.

FIG. 2. MR imaging at time of visual loss in the right eye. A: Unenhanced proton density-weighted axial image at level of carotid bifurcation shows no evidence of mass. B: Unenhanced proton density-weighted axial image at slightly higher level also shows no evidence of a mass. C: Unenhanced T1-weighted sagittal image shows no evidence of a mass in the region of the intracranial portion of the right optic nerve.
FIG. 3. MR imaging two months after onset of visual loss in the right eye. A: Unenhanced proton density-weighted axial image in same plane as Fig. 2A now shows a large mass consistent with a giant aneurysm in the right basal frontal region. B: Unenhanced T1-weighted sagittal image in same plane as Fig. 2C shows a heterogeneous mass with high signal intensity compared with brain, obliterating the right side of the suprasellar cistern. Note that the intracranial portion of the optic nerve cannot be seen.

DISCUSSION

This case is of significance for several reasons. First, it emphasizes that aneurysms that are large enough to produce loss of vision by compression of the intracranial portion of the optic nerve may nevertheless be too small to be detected by MR imaging. The patient described in this report underwent MR imaging at the time of initial loss of vision in the right eye. A retrospective review of all available films by both the original neuroradiologist and two independent neuroradiologists failed to identify the aneurysm that eventually was found to have caused the optic neuropathy.

Day reviewed 80 cases of carotid-ophthalmic aneurysms and concluded that unruptured aneurysms smaller than 10 mm do not produce visual symptoms (4); Satoh and Kadoya studied 32 angiographically or surgically proven intracranial aneurysms using both computed tomographic (CT) scanning and MR imaging and found that MR imaging detected only four of six aneurysms (67%) whose diameter was larger than 9 mm (5). In addition, neuroimaging detected only nine of 18 aneurysms (50%) whose diameter was 5-9 mm and no aneurysm whose diameter was less than 4 mm. Other authors have reported similar findings (6). Thus, even if it is true that a carotid-ophthalmic aneurysm must be at least 10 mm in diameter before it causes visual symptoms, such an aneurysm nevertheless may not be detected by MR imaging, and if aneurysms less than 10 mm can, in fact, cause visual symptoms, there is an even greater probability that such an aneurysm would be undetected by MR imaging. Cerebral angiography remains the most sensitive method of detecting an intracranial aneurysm.

A second issue raised by this case is the rapidity with which an intracranial aneurysm apparently expanded to a considerable size. It is generally believed that the formation of a giant intracranial aneurysm may take years (7-9). In our case, however, there was rapid enlargement of an untreated aneurysm that initially was probably 10 mm in size or less to a size of 25 mm over eight weeks. Other authors have also documented rapid enlargement of intracranial aneurysms, some to giant size.

Bull described a 51-year-old man with a four-year history of difficulty with speech and recent episodes of drowsiness and syncope, who was found to have a "very large" aneurysm arising near the bifurcation of the left internal carotid artery (10). The patient underwent ligation of the left common carotid artery; however, he developed worsening neurologic symptoms and signs over the next six months, and repeat neuroimaging studies showed what was interpreted as further enlargement of the lesion. A craniotomy was per-
FIG. 4. Visual field of left eye at time of presentation to the Johns Hopkins Hospital. Kinetic perimetry shows an incomplete temporal hemianopia that is denser superiority than inferiorly. Visual acuity in the eye is 20/30. The right eye is blind.

formed, and the aneurysm was excised. It measured $52 \times 42 \times 38$ mm and was filled with laminated thrombus.

Fried and Yballe reported the case of a 46-year-old man who developed severe headache, nausea, vomiting, and nuchal rigidity (11). A large lumbar puncture demonstrated grossly bloody cerebrospinal fluid, and cerebral angiography disclosed a $15 \times 15$-mm aneurysm arising from the left anterior cerebral artery. The patient deteriorated rapidly and then became comatose. A repeat angiogram one week later showed enlargement of the aneurysm associated with an intracerebral hematoma. The patient underwent craniotomy, evacuation of the hematoma, and clipping of the aneurysm; however, he never recovered from surgery and died ten weeks later. Postmortem examination revealed a giant aneurysm arising at the junction of the anterior communicating and left anterior cerebral arteries. The aneurysm measured $50 \times 70 \times 70$ mm.

Finally, Weir and Drake reported the case of a 34-year-old woman in the 20th week of pregnancy who experienced sudden dizziness, diplopia, and headache (12). Cerebral angiography showed an $8 \times 5 \times 7$-mm aneurysm in the region of the right superior cerebellar artery. The patient underwent craniotomy and attempted clipping of the aneurysm; however, the neck of the aneurysm could not be delineated, and the aneurysm was therefore not clipped. Postoperatively, MR imaging disclosed a $13 \times 13 \times 10$-mm partially thrombosed aneurysm. One week later, a second craniotomy was performed, at which time the aneurysm was partially clipped. After the second operation, the patient seemed well; however, 16 weeks later, she experienced acute headache, drowsiness, confusion, and a left oculomotor nerve paresis. Repeat angiography now showed that the aneurysm had enlarged in size, and the filling portion now measured $32 \times 12 \times 12$ mm. Balloon embolization of the aneurysm was attempted but was unsuccessful. Accordingly, a third craniotomy was performed, and the basilar artery was occluded with an aneurysm clip just below the origin of the superior cerebellar artery.

A number of mechanisms seem to contribute to the growth of an unruptured intracranial aneurysm. Initially, a preexisting gap in the tunica media at the bifurcation of a cerebral artery can no longer resist the impact of the bloodstream. A saculation is thus formed, which extends to form a small aneurysm with a thin dome and a thin neck (13,14). Because of turbulent blood flow in a relatively inelastic sac, endothelial damage occurs, leading to mural thrombosis. After a period of thrombogenesis, further growth follows, with organization of the thrombus and proliferation of tis-
FIG. 5. Right internal carotid arteriogram, lateral (A) and oblique (B) views, performed at time of presentation to Johns Hopkins Hospital, shows marked narrowing and stretching of the supraclinoid portion of the right internal carotid artery (large arrowhead), consistent with a significantly clotted aneurysm arising from the right internal carotid artery near the origin of the ophthalmic artery. Note the slight blush that represents flow within the aneurysm on the oblique view (small arrowhead).

Sue in the intima caused by mechanical stimulation from the bloodstream (14,15). Stasis within the sac and mural thrombosis eventually cause ischemia in the wall of the aneurysm; the dome and neck of the aneurysm then thicken; and the sac enlarges (11). In addition, however, it has been postulated that central clotting with preservation of peripheral blood flow within an aneurysm causes persis-

FIG. 6. Visual field of left eye after ligation of the right internal carotid artery in the neck and placement of a clip across the supraclinoid portion of the artery, distal to the origin of the ophthalmic artery. Kinetic perimetry reveals relative superotemporal defect. Visual acuity in the eye has improved to 20/25. The right eye is still blind.
tent hemodynamic injury to the wall, leading to scar formation and enlargement of the aneurysm (16). After rupture of an intracranial aneurysm, further growth may occur not only from the mechanisms described above but also from expansion of the wall of the aneurysm at the site of rupture, where there is only a thin protective layer of fibrin and other blood products, and from recurrent hemorrhage from capillaries that develop within the new wall and weaken it (11). Although these processes generally occur slowly over several years (11), the process may be rapidly progressive, with marked enlargement of the aneurysm over a few months, as evidenced by our case and those of others (7, 10, 12).

A final issue raised by this case is the importance of close follow-up in any patient with a clinical diagnosis of optic neuritis, regardless of the results of neuroimaging. This patient's history and clinical findings met the criteria for him to be included in the ONTT, which had stringent requirements for entry. Despite the clinical diagnosis of optic neuritis and normal MR imaging, the patient's subsequent clinical course and neuroimaging findings ultimately showed that his loss of vision had been caused by compression of the optic nerve by an intracranial aneurysm and not by demyelination. Several authors have reported similar cases in which an intracranial aneurysm has caused an optic neuropathy with features that mimic an acute retrobulbar optic neuritis, including sudden loss of vision in one eye, retrobulbar pain, a central visual field defect, an ipsilateral relative afferent papillary defect, and a normal-appearing optic disc (17–19). Although the percentage of patients with signs and symptoms suggesting acute optic neuritis who actually have an intracranial mass lesion as the cause of their optic neuropathy is less than 0.5% (1), the possibility of such a lesion must nevertheless be considered in every patient, particularly if he or she presents atypically or has an atypical course, and the physician caring for such a patient must even be prepared to repeat diagnostic studies in such cases.

REFERENCES


Simultaneous, Multiple Cranial Neuropathies in Diabetes Mellitus

Calvin G. Eshbaugh, M.D., R. Michael Siatkowski, M.D., J. Lawton Smith, M.D., and Lanning B. Kline, M.D.

Cranial mononeuropathies, particularly ophthalmoplegia and facial palsy, are common entities in the diabetic population. Simultaneous multiple cranial neuropathies due to diabetes are much less common, however. We present three patients with this entity.

**Key Words:** Diabetes—Cranial neuropathy.

**CASE REPORTS**

**Case 1**

A 73-year-old man with a 2-year history of non-insulin-dependent diabetes developed a right facial palsy in September 1991, for which he was treated with prednisone. In December of the same year, he experienced the acute onset of binocular diplopia and was found by his local ophthalmologist to have right third and sixth nerve palsies; the pupill and lid were normal at that time. One month later, right ptosis developed.

Past medical history was significant for hypercholesterolemia and a left cerebellar infarction 2 years previously with no sequelae. In 1982 he had a pupil-sparing left third nerve palsy, which cleared in 2 months. In 1985 he developed left trigeminal neuralgia for which he underwent rhizotomy 3 years later.

On examination in January 1992, visual acuity was 20/30 OD, 20/20 OS. Pupils were 3.5 mm, round, and 3+ reactive to light without afferent defect. The right lid fissure measured 3 mm, left 9 mm. A peripheral right facial nerve palsy was present with a paralytic ectropion. The left eye had full motility. In the right eye there was a 75% abduction deficit, inability to adduct past the midline, and 80–90% limitation of both depression and elevation (Fig. 1A–D). Forced ductions were negative. On attempted gaze down and left, there was no intorsion of the right eye, consistent with paresis of the superior oblique. Trigeminal sensation was equal in all three divisions bilaterally. The fundi were normal with no sign of diabetic retinopathy.

Tensilon test, Lyme titers, RPR, FTA-Abs, CBC, and lumbar puncture were all normal. Two MRIs of the brain revealed an old left cerebellar infarct, but normal cavernous sinuses and brain stem.

On follow-up examination 2 months later, the right lid fissure measured 7.5 mm, and the facial
nerve paresis had almost completely resolved. Abduction of the right eye was 90-95% of normal, depression and elevation were full, and adduction was approximately 90% of normal (Fig. 2A-C). Motility in the field of action of the right superior oblique muscle was full, and no cyclodeviation was noted on double Maddox rod testing. The patient showed complete resolution of all ocular findings after an additional 2 months.

Case 2

A 58-year-old white male with no significant past medical history developed binocular diplopia on December 25, 1991. In January 1992 he noted drooping of the left upper eyelid, followed by left facial drooping one month later.

Examination revealed visual acuity of 20/25 OD, 20/30 OS. Pupils were 4 mm, round, and 3+ reactive to light bilaterally without afferent defect. The right lid fissure measured 9 mm, the left 4 mm. A peripheral right facial nerve paresis was present. Abduction was 25% of normal bilaterally. The left eye did not adduct past midline and had 50% elevation and depression deficits. No intorsion of the left eye was noted in gaze down and right. Trigeminal function was intact bilaterally.
The fundi were normal with no sign of diabetic retinopathy.

Two months after his initial presentation, pupils were 4.5 mm, round, and 3+ reactive. He had a mild residual right facial nerve palsy with only slight flattening of the right nasolabial fold. Motility was normal but for 10% abduction deficits bilaterally.

Forced ductions, Tensilon test, and brain CT and MRI were normal. Serum RPR, FTA-Abs, Lyme titers, and CBC were all normal, but serum glucose was 482 mg/dl. Lumbar puncture revealed an elevated glucose of 190 mg/dl, but was otherwise normal. The patient was hospitalized and glycemic control achieved in 3 days. He had complete clearing of his ophthalmic findings within 5 months after onset.

Case 3

A 71-year-old man with an 8-year history of insulin-dependent diabetes developed the sudden onset of diplopia followed by complete left ptosis in May 1985. Visual acuity was 20/30 OU. The pupils measured 3.5 mm OD and 4.5 mm OS, but were equally reactive to light without afferent defect. There was complete left ptosis. The right eye moved normally but the left had total abduction and adduction deficits, as well as no function in the field of the inferior rectus. Trigeminal function was intact bilaterally. The fundi showed no signs of diabetic retinopathy. Forced ductions were negative. Brain CT was normal. By mid-September 1985, oculomotility and levator function were normal.

DISCUSSION

The first reported case of diabetic ophthalmoplegia was in 1866 (1). Although diabetic cranial neuropathy is commonly encountered in ophthalmologic practice, data on its prevalence are scarce. Waite and Beetham reported a 0.4% prevalence (16 of 4,001 patients) of paresis of one or more extraocular muscles over a 10-year period following the initial diagnosis of diabetes (2). A large retrospective series from the Institute for Diabetes Care and Research in Tokyo showed a 0.97% incidence of cranial nerve 3, 4, 6, or 7 palsies in the diabetic population over a 25-year period (3), 7.5 times more frequent than in the nondiabetic control group. Only two of their patients had simultaneous neuropathies, both oculomotor and abducens. All patients experienced complete, spontaneous recoveries, with the mean recovery time for the ophthalmoplegia being 11.9 weeks.

If approximately 0.5-1.0% of diabetics will sustain a cranial neuropathy over a 25-year period, the next question becomes: Of all patients with cranial nerve palsies, how many are secondary to diabetes? The Mayo Clinic has reported a large series of patients with cranial neuropathies affecting cranial nerves 3, 4, and 6. Their cumulative experience to date consists of over 4,000 patients (4). Of all cases, the abducens nerve was by far the most commonly
involved (43.9% of cases), followed by the oculo-
motor nerve (28.0%), trochlear nerve (15.0%), and
multiple simultaneous ocular motor palsies
(13.1%). After excluding 102 cases due to congeni-
tal insults, just over 15% of the remaining cranial
neuropathies were attributed to vascular causes
(including diabetes, hypertension, atherosclerosis,
vasculitis). Of the patients with multiple simulta-
eous ocular motor palsies, neoplasm was by far
the most common cause (33.3%), with vascular be-
ing significantly rarer (4.1%). [These data pertain
to adults only, as in the pediatric population, vas-
ular cranial neuropathies are exceedingly rare (5).

From further calculation, one can determine that
20% of patients with multiple simultaneous cranial
neuropathies attributed to a vascular cause had di-
betes mellitus at the onset of ophthalmoplegia
(0.8% of all patients with simultaneous polyneu-
ropathy). One should note that the Mayo series, if
anything, underestimates the frequency of dia-
betes in their group, because information is included
only for those patients with previously diagnosed
disease; in all likelihood, some patients had their
cranial neuropathies as the initial manifestation of
diabetes.

Even if a patient is not a known diabetic and has
a negative workup at the onset of the cranial neu-
ropathy, the future development of diabetes mel-
litus remains a distinct possibility. Goldstein and
Cogan reported on 33 patients with isolated ocu-
alomotor nerve palsy (6). Thirty percent of them
were previously diagnosed diabetics. In three of
the 33 (10%), the third nerve palsy was the pre-
senting sign of diabetes. Another 20% of them
would have glucose intolerance by today's defini-
tion, with one of these patients going on to de-
velop frank diabetes within 4 years. [Glucose in-
tolerance is defined as serum glucose: 115-140 mg/
dl at fasting, or 0.5 h after a 75-g carbohydrate
load; and/or >200 mg/dl 1 h after similar load; and/
or 140-199 mg/dl 1.5, 2, or 3 h after similar load
(7).] Since at least 25% of patients with abnormal
glucose-tolerance testing will develop diabetes
within 5 years (8) and up to 50% within 16 years
(7), then by these criteria at least 35% of patients
with third nerve palsy of vascular or undeter-
mined origin will become diabetic. Green attrib-
uted almost 20% of 130 cases of third nerve palsy
to diabetes (9). In half of these cases, the oculomo-
tor nerve palsy was the first sign of diabetes. Glu-
cose tolerance testing is thus necessary during the
initial workup of a patient with a cranial neurropa-
thy of unknown etiology, and diabetes mellitus
must be continually considered as long as the
cause of the neuropathy remains obscure.

The recurrent nature of diabetic cranial neuropa-
athy has been well described and is evidenced by
our first case. One of the most fascinating cases
reported describes a woman who suffered 13 sep-
arate episodes of single or multiple cranial nerve
palsies over an 18-year period, all with full recov-
ery (10). The recurrent nature of cranial nerve pal-
sies in diabetics does not seem to bode poorly for
their prognosis. Most of these patients also recover
fully; in fact, the mean recovery time was briefer
for the later episodes than for the first (6,11,12).

Although simultaneous diabetic cranial poly-
neuropathy is much rarer, when it occurs, the
third cranial nerve seems to be the most frequently
involved. Table 1 shows the cases of multiple si-
taneous diabetic cranial neuropathies in the lit-

erature. To our knowledge, only nine other pa-
tients with this entity have been previously de-
scribed (1,3,10,12-14). The mean age of the
patients (57.6 years) and mean recovery time (13.7
weeks) do not significantly differ from those pa-
tients with isolated or recurrent diabetic cranial
mononeuropathy.

Sergott et al. have elucidated the following clin-
ic dictum: "... a diabetic is permitted one cranial
neuropathy at a time. Exceptions to this rule, ei-
ther more than one motor nerve per eye, or simul-
taneous bilateral cranial palsies, make investiga-
tion mandatory" (12). Therefore, clinical consider-
ations in a patient with simultaneous multiple
cranial neuropathies must include but are not
limited to: myasthenia gravis, cranial arteritis, thy-
roid eye disease, Miller-Fisher variant of Guillain-
Barre, neoplasm, basilar artery aneurysm or occlu-
sion, chronic meningeval inflammation, and diabe-
tes mellitus. Appropriate diagnostic workup would
include forced ductions, Tensilon test, erythrocyte
sedimentation rate, glucose tolerance testing, neu-
roimaging, and CSF analysis.

The culprit lesions in diabetic cranial neuropathy
may occur anywhere from the brain stem to the
orbit. Dreyfus et al. reported histopathology show-
ing myelin sheath and axonal destruction in the
oculomotor nerve of a diabetic who died before
resolution of a third nerve palsy (15). Involvement
of the intracavernous portion (16), as well as the
subarachnoid segment of the nerve (17), has been
reported. There is also evidence that the lesions in
diabetic cranial neuropathies may be intraparen-
chymal. Hopf and Gutmann described 24 diabetics
with oculomotor nerve palsy (75% pupil-sparing),
impaired masseter reflex, and brain stem involve-
ment based on MRI findings (18). Fukutake and
Hirayama reported a case of an abducens nerve
palsy in a diabetic from a pontine infarct (19).
NEUROPATHIES IN DIABETES

Breen et al. noted two cases of midbrain infarcts causing pupil-sparing oculomotor nerve palsies (20). Usui et al. (21) reported on a diabetic with right third and fourth nerve palsies. At postmortem examination, the intracavernous portions of the oculomotor, trochlear, and abducens intraneural vasculature revealed marked thickening and proliferation within the intimal layers (21). Bregman and Harbour reported a superior division diabetic oculomotor nerve palsy (22), and Cunningham and Good a corollary case of inferior branch oculomotor palsy (23), implicating orbital involvement of the nerve.

Without histopathology, the exact site and nature of the lesions responsible for simultaneous diabetic cranial neuropathies remain unknown. Luco and Valenzuela (13) speculated that since the oculomotor nerve fibers have common nutrient vessels in the cavernous sinus (specifically the meningohypophyseal trunk and the inferior artery of the cavernous sinus, both branches of the internal carotid artery), an occlusion of one of these vessels could lead to ischemia of all three ocular motor nerves. Alternatively, diffuse posterior fossa ischemia is another possible pathogenesis. Of note is that none of our three patients had severe hyperglycemia or evidence of diabetic ketoacidosis or nonketotic hyperosmolar coma. Similarly, none of our patients had any diabetic retinopathy. It thus seems likely that the occurrence of simultaneous multiple cranial neuropathies is related more to the location of the lesion(s) rather than to the diffuse long-term effects of diabetes on vascular integrity. Although the proximity of the ocular motor nerves in the cavernous sinus tends to implicate this area anatomically, it does not account for the concomitant occurrence of peripheral facial palsies in these patients.

Diabetes mellitus is a rare but benign cause of multiple and/or bilateral simultaneous cranial neuropathies. This entity may be the presenting sign of diabetes and often occurs in the complete absence of diabetic retinopathy. Although the prognosis is excellent, it remains a diagnosis of exclusion and retrospection.

REFERENCES

Cavernous Sinus Hemangioma
Clinical and Neuroimaging Features

Andrew G. Lee, M.D., Neil R. Miller, M.D., Paul W. Brazis, M.D., and Mark L. Benson, M.D.

A patient presented with an isolated left sixth nerve palsy. Magnetic resonance imaging revealed a sharply marginated 3 cm lesion in the left cavernous sinus, which was isointense to gray matter on T1-weighted images, hyperintense on T2-weighted images, and enhanced with paramagnetic contrast material. Cerebral angiography showed a homogenous blush fed by an enlarged meningohypophyseal artery. The neuroimaging findings were thought to be most consistent with the diagnosis of a cavernous sinus meningioma. At the time of surgery, a vascular mass was encountered, and a biopsy was consistent with a cavernous hemangioma. This report describes the clinical and neuroimaging features of cavernous sinus hemangiomas that may help to differentiate them from other cavernous sinus lesions.

Key Words: Cavernous hemangioma—Cavernous sinus—Magnetic resonance imaging.

Cavernous hemangiomas are vascular hamartomas that occasionally arise in the cavernous sinus (1,2) and that represent about 3% of all benign tumors in this region (3). This report describes the clinical and neuroimaging features of cavernous sinus hemangiomas that may help to differentiate them from other cavernous sinus lesions.

CASE REPORT

A 31-year-old woman presented with a 2-month history of binocular horizontal diplopia, worse on gaze to the left. There was no clear precipitant for the onset of her symptoms, and she had no other systemic or neurologic complaints. Past medical history was significant for well-differentiated papillary carcinoma of the thyroid gland with metastasis to one paratracheal lymph node diagnosed 11 years earlier. This was treated with total thyreectomy and right modified radical neck dissection. She had been followed at regular intervals by her medical doctor and had no evidence of recurrence or metastasis at presentation.

General physical examination was normal except for a surgical scar on the neck with excavation of both supraclavicular fossae, right more than left. Visual acuity, color vision, visual fields, and pupillary reactions to light and near stimuli were normal. Corneal and facial sensation were normal. Motility examination showed reduced abduction of the left eye (55 degrees in the left eye versus 75 degrees in the right eye). In primary position, the patient had an esophoria of 6 prism diopters. On gaze to the right, there was an esophoria of 8 prism diopters and on gaze to the left, there was an esotropia of 20 prism diopters. The ocular fundi were normal. A diagnosis of an isolated left abducens nerve paresis was made.

Magnetic resonance (MR) imaging of the brain
revealed a sharply marginated, 3-cm lesion in the left cavernous sinus that was isointense to gray matter on T1-weighted MR images (Fig. 1). Following intravenous administration of gadolinium-DTPA, the mass enhanced markedly (Fig. 2). The mass was hyperintense on proton-density (Fig. 3) and T2-weighted images, surrounded the intracavernous portion of the left internal carotid artery and extended into the sella turcica. A few curvilinear flow voids were seen within the tumor, suggesting small vessels.

Cerebral angiography showed a hypervascular mass within the left cavernous sinus with upward displacement of the intracavernous portion of the left internal carotid artery. The vascular supply to the mass originated from meningohypophyseal branches of the left internal carotid artery (Fig. 4). There was no evidence for vascular supply from the external carotid artery.

**COURSE**

A preliminary diagnosis of cavernous sinus meningioma was made, and the patient underwent a left pterional craniotomy, at which time the neurosurgeon encountered a dark vascular mass that was biopsied.

Frozen section of the lesion was consistent with a vascular hamartoma, and therefore the surgeon elected not to attempt removal of the remainder of the mass. Permanent pathologic sections revealed numerous irregular vascular channels lined by endothelium and separated by a fibroconnective tissue stroma consistent with a cavernous angioma (Fig. 5). The specimen demonstrated markedly positive staining for factor VIII of the endothelial walls of the vascular channels, further supporting the diagnosis of an angioma.

Postoperatively, the patient had a persistent left abducens nerve paresis, a left Horner syndrome, and left-sided sensory loss in the cutaneous distribution of the ophthalmic division of the trigeminal nerve.

**DISCUSSION**

Cavernous hemangiomas only rarely arise in the cavernous sinus, predominantly occurring in women (94%) (4) in the fifth decade of life (5). Al-
though benign, cavernous hemangiomas may cause retrobulbar pain, facial numbness, ophthalmoplegia, or a combination of these findings while they are still fairly small (1,5). Alternatively, they may remain asymptomatic until they are very large, at which time they may produce signs and symptoms of a typical cavernous sinus syndrome. If they extend superiorly, hypothalamic manifestations such as weight gain, decreased libido, or increased thirst may occur (1,3,4,6). Symptoms may fluctuate, becoming more pronounced during periods of strenuous physical activity, perhaps related to vascular engorgement of the tumor within the cavernous sinus (7). Occasionally, hemorrhage within the tumor may cause sudden onset or exacerbation of symptoms and signs.

Neuroimaging studies may be helpful in the diagnosis of cavernous sinus hemangioma. Computed tomographic (CT) scans usually show a well-demarcated, homogeneously enhancing mass that may be indistinguishable from a meningioma (2,8). However, the lesion characteristically is not calcified, and the surrounding bone typically demonstrates erosion or remodeling, rather than hyperostosis. The presence of calcium within the lesion or associated hyperostosis on CT scanning thus favors meningioma, although the absence of these findings does not necessarily differentiate between the two lesions (3).

Although MR imaging of intracranial hemangiomas usually reveals characteristic changes—iso- or hypointensity on T1-weighted images; iso- or hyperintensity on T2-weighted images; a "reticulated" appearing core of mixed signal intensity on T2-weighted images; a prominent hypointense rim on T1- and T2-weighted images; and nonhomogeneous enhancement after intravenous administration of paramagnetic contrast material—these features are uncommonly seen with hemangiomas in the cavernous sinus (2). Instead, such lesions usually show a homogeneous signal intensity on unenhanced T1- and T2-weighted images and marked enhancement after the intravenous administration of paramagnetic contrast material. This radiographic pattern was seen in our patient and was thought to be most consistent with a meningioma.

Like CT scanning and MR imaging, cerebral angiography may or may not be helpful in distinguishing cavernous hemangiomas from other lesions in the cavernous sinus. One-third of cavernous sinus hemangiomas are angiographically
silent, showing no staining or abnormal vasculature (2). The remainder of cases show a typical tumor blush that often has a flecked appearance associated with pooling of contrast in small collections or lakes (3). This appearance is apparently caused by the reduced blood flow throughout the lesion (2,8,9). The most commonly identified feeding arteries are the artery of the inferior cavernous sinus, the meningohypophyseal trunk, the middle meningeal artery, and the accessory middle meningeal artery. In our patient, the angiographic appearance, like the MR imaging, was thought to be most consistent with a meningioma.

Cavernous sinus hemangiomas must be differentiated from the two most common benign intracavernous neoplasms: meningiomas and schwannomas. Indeed, most of the reported cases of intracavernous hemangioma were thought to be meningiomas until surgery was performed (1,5,8,10). As noted above, the presence on CT scanning of calcium within the lesion and hyperostosis of surrounding bone are features that strongly suggest the diagnosis of meningioma. Lack of a tumor blush on angiography favors a diagnosis of schwannoma as does the presence of an enlarged foramen ovale or foramen rotundum (3,11). The MR features of meningiomas, schwannomas, and intracavernous hemangiomas are quite similar, however, and may not permit differentiation among these lesions.

In many cases of intracavernous hemangioma, the correct diagnosis cannot be made until a biopsy of the lesion is performed and frozen sections are obtained that show the characteristic pathologic features of the lesion. The correct diagnosis is crucial, since attempted removal of cavernous sinus hemangiomas may be associated with a substantial morbidity and mortality, primarily related to severe uncontrollable hemorrhage (3). Linskey and Sekhar reviewed the literature in 1992 and reported on 52 operative cases. Of these 52 cases, bleeding was described as a “problem” in 21 cases (42%), “massive or severe” in 15 cases (29%), and severe enough to require discontinuation of surgery in 3 cases (6%). In addition, these authors reported the results of cranial neuropathies in 27 patients after surgery. Cranial neuropathies worsened after surgery in 12 patients (44%), remained the same in 4 patients (15%), and improved in 11 patients (41%) (3). Removal of the lesion may require preoperative balloon occlusion of the ipsilateral internal or external carotid artery or even preoperative radiation therapy.

There have been several reports that cavernous hemangiomas may be radiosensitive (5). Several cases treated with conventional radiotherapy have been reported (3,5). Indeed, our patient was treated with conventional fractionated radiotherapy of 4,500 cGy with gradual improvement of her signs and symptoms. There is, however, no long-term prospective data regarding the efficacy of this treatment. The potential role of stereotactic radiosurgery in these tumors has yet to be clearly defined (5). Nevertheless, the physician dealing with these lesions must be aware of all treatment options.

REFERENCES

Vertical Gaze Paralysis and Intermittent Unresponsiveness in a Patient with a Thalamomesencephalic Stroke

David Q. Beversdorf, M.D., Lawrence R. Jenkyn, M.D., John T. Petrowski III, O.D., Laurence D. Cromwell, M.D., and Richard E. Nordgren, M.D.

A patient with paralysis of upward gaze and downward gaze, absent oculocephalic reflexes, and absent vertical saccades also demonstrated intermittent stupor over the first 9 days of presentation. Magnetic resonance imaging (MRI) demonstrated an infarct in the tegmentum of the mesencephalon including the right red nucleus and the periaqueductal area, superior to the oculomotor nucleus, and contiguous through the left thalamus. The infarct included the area around the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF), as well as the midbrain reticular formation. Mechanisms are proposed for the unusual concurrent sign of intermittent unresponsiveness in this case.

Key Words: Vertical gaze palsy—Stroke—Rostral interstitial nucleus of the medial longitudinal fasciculus—Parinaud's syndrome—Unresponsiveness.

Vertical gaze paralysis is often associated with a variety of other neurological signs, such as those of Parinaud's syndrome (1-3) (pupillary light-near dissociation, lid retraction, ocular skew deviation, retraction nystagmus, or downward gaze; however, the definitions in the literature are variable). The combination of paralysis of downward and upward gaze has been localized to unilateral lesions of the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF), located in the tegmentum of the midbrain within the midbrain reticular formation (4,5). We report a case in which intermittent unresponsiveness is a prominent feature of vertical gaze paralysis.

CASE REPORT

A 76-year-old woman with a past medical history significant for non-insulin dependent diabetes mellitus, hypertension, asthma, and a remote history of tobacco smoking, was seen in an area hospital after awakening in the morning with slurred speech, sluggishness, and dizziness. On evaluation, the patient's arousal level had deteriorated to semipurposeful responses only to painful stimuli. The right pupil at that time was reported as fixed and midposition, whereas the left responded fully. The patient's arousal improved to the point of appropriately discussing politics several minutes later. Over the next 24 h, the patient had two further episodes of similar loss of arousal with rapid recovery. Over that same period, the patient had noticed some right-sided weakness and had once mentioned difficulty with her vision. The patient was then transferred to Dartmouth-
Hitchcock Medical Center (DHMC). On arrival, the patient was arousable to painful stimuli and would quickly drift back to sleep. The patient would say only “yes,” “no,” or “leave me alone.” The patient’s right pupil was minimally reactive and 4 mm, whereas her left pupil was 1.5 mm and sluggishly reactive. Extraocular muscles were reported as normal at that time, and her extremities appeared to move symmetrically. Reflexes and response to pinprick were also symmetric.

Two days after admission, the patient remained confused, believing the year to be 1939, but was fully alert. The patient complained of inability to see below midline. Her visual fields were found to be intact, but there was complete bilateral paralysis of upgaze and downgaze, including absent vertical oculocephalic reflexes. Horizontal gaze was intact to voluntary and reflex (oculocephalic) testing. Once on her third day of hospitalization and twice on her fourth day, the patient again had episodes of decreased arousal. Her blood pressure was found to be elevated during these episodes (to 212/122 on one occasion), and the patient was again only minimally arousable at these times, demonstrating semipurposeful movement to noxious stimuli. At no point was the patient given the benzodiazepine antagonist flumazenil. Each episode lasted ~30 min, and there were no abnormalities in her heart rate, heart rhythm, temperature, respirations, or oxygen saturation. The patient’s pupils would constrict to pinpoint diameter during these episodes. The patient had no further episodes after the fourth hospital day, and her baseline confusion cleared over the next several days. She had no recall of her events. The patient was discharged home 9 days after admission with complete bilateral loss of upward and downward gaze, including oculocephalics. The patient also continued to have small pupils, 2 mm and reactive bilaterally. These ocular findings persisted at her 2-month follow-up visit, although minimal recovery of downgaze occurred. At the follow-up examination, vertical saccades could not be induced using an optokinetic nystagmus (OKN) stripe drum. Bell’s reflex (eyes deviating upward with lid closure) was absent bilaterally. The patient demonstrated a mild exophoria at distance on cover testing. At near, the patient was unable to converge and manifested a small-angle exotropia. The angle of the tropia was the same in all directions of lateral gaze, ruling out a muscle or cranial nerve paresis. Formal visual fields were normal for the patient’s age.

Studies while in hospital included an electrocardiogram, demonstrating normal sinus rhythm and a right bundle branch block. Prothrombin time was 11.8 s with an international normalized ratio of 1.06. Partial thromboplastin time was 21 s. Hemoglobin was 12.7 g/dl; hematocrit, 38%; white blood cell count, 9,000; and platelet count, 393,000. Sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, calcium, magnesium, and phosphorus were within normal range. Erythrocyte sedimentation rate was 44 mm/h. None of

FIG. 1. T-2 weighted magnetic resonance image (MRI) of the lesion (white arrows) in our case. A: Infarct on the left side of the superior thalamus. B: Bilateral infarct of the inferior thalamus, left more extensive than right. C: Infarct on the right side of the midbrain involving the red nucleus, the area around the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) and a portion of the reticular activating system (left-right orientation is opposite of that of the schematic representation in Fig. 2).
These laboratory values varied significantly throughout her stay, and her blood sugar remained in the 100s or 200s (mg/dl), including testing during her episodes. The patient's arterial blood gas panel revealed a pH of 7.37, a partial \( \text{CO}_2 \) pressure of 49 mm Hg, and a partial \( \text{O}_2 \) pressure of 64 mm Hg, which are within normal range.

The patient's liver function tests and thyroid function tests were within normal limits. Her urinalysis was remarkable only for protein, and her urine culture was negative. Cerebrospinal fluid (CSF) pressure, protein, and glucose were normal, and there was no xanthochromia. One white blood cell was observed on CSF smear, and all other stains and cultures (routine, fungal, and acid-fast bacillus) were negative. CSF cryptococcal antigen and VDRL were also negative. Echocardiography showed left ventricular hypertrophy consistent with her history of hypertension, and continuous electrocardiographic monitoring did not reveal any dysrhythmias (including during an episode). An EKG demonstrated intermittent frontal delta rhythm activity. Metanephrines, vanillylmandelic acid, and urine catecholamines were negative. Computed tomography (CT) and magnetic resonance imaging (MRI) (fig. 1) demonstrated an infarct in the left thalamus and in the right midbrain superior to the oculomotor nucleus, including the red nucleus (as well as the area around the riMLF). This infarct was contiguous through the thalamomesencephalic periaqueductal area. Carotid Dopplers revealed 16–49% stenosis of both common carotid arteries as well as the left internal carotid. The right internal carotid artery was 50–79% stenosed. Vertebrals had anterograde flow. The patient declined cerebrovascular angiography.

### TABLE 1. Summary of related cases in the literature

<table>
<thead>
<tr>
<th>Cases</th>
<th>Lesion</th>
<th>Reflexes</th>
<th>Level of consciousness</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moriya et al. (7)</td>
<td>Unilateral infarct riMLF</td>
<td>Oculocapillaries retained</td>
<td>No change</td>
<td>Convergence nystagmus</td>
</tr>
<tr>
<td>Yamamoto (8)</td>
<td>Bilateral infarct thalamomesencephalic junction</td>
<td>Oculocapillaries limited</td>
<td>No change</td>
<td>—</td>
</tr>
<tr>
<td>Ranalli et al. (9)</td>
<td>riMLF, nD, motor pole ISC</td>
<td></td>
<td>Only initially impaired (with cardiac event)</td>
<td>Pupillary responses normal, eyes down with eye closure</td>
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<tr>
<td>Segarra, case 2 (10)</td>
<td>Midbrain infarct superior to oculomotor nerve</td>
<td></td>
<td>Coma, then lethargy and &quot;akinetic mutism of mesencephalic origin&quot;</td>
<td>Dilation pupils</td>
</tr>
<tr>
<td>Pierrot-Deseilligny et al., case 6 (11)</td>
<td>Small bilateral thalamic infarcts, left &gt; right</td>
<td>Oculocapillaries retained</td>
<td>Coma, then memory loss</td>
<td>Pupillary responses normal</td>
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<tr>
<td>Pierrot-Deseilligny et al., case 6 (11)</td>
<td>Dorsomedial thalamic lesions</td>
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<tr>
<td>Mills and Swanson (12)</td>
<td>Left midbrain and lower thalamus infarcts</td>
<td>Oculocapillaries retained</td>
<td>Coma, then memory loss</td>
<td>Pupillary responses normal</td>
</tr>
<tr>
<td>Wall et al. (13)</td>
<td>Bilateral destruction of riMLF (nD and nC preserved)</td>
<td></td>
<td>Vertical saccades absent on ENG, pupillary responses normal, eyes up with eye closure</td>
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<td>Jenkyn et al. (14)</td>
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<td>Böttner-Ennever et al. (15)</td>
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<td>Ataxia, poorly responsive pupils</td>
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<td>Bogousslavsky et al. (16)</td>
<td>Right riMLF</td>
<td></td>
<td>Incomplete bilateral internuclear opthalmoplegia</td>
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<tr>
<td>This case</td>
<td>Bilateral infarct thalamomesencephalic junction</td>
<td>Vertical oculocapillaries retained, OKN lost</td>
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<td>Pupillary responses normal</td>
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ENG, electronystagmogram.
**DISCUSSION**

Complete bilateral paralysis of upgaze and downgaze [considered by some a variant of the Parinaud syndrome, or the pretectal syndrome (6)] has been localized by Bogousslavsky et al. (4) to a unilateral lesion of the riMLF, not involving the nucleus of Darkschewitsch (nD) or interstitial nucleus of Cajal (iC). In that report, however, the pupillary reflexes could not be defined because of trauma from cataract surgeries. Therefore, full correlation with our case with small and reactive pupils cannot be made, although our MRI findings do help with correlation. Several important distinctions should be made between the case of Bogousslavsky et al. (4) and our case. Our case had intermittent impairment of arousal, whereas their case did not describe any alteration in consciousness. Furthermore, the lesion in our case was significantly more widespread. In the case of Bogousslavsky et al. (4), vertical optokinetic testing with a drum failed to elicit a response, but oculocephalic maneuvers led to a full response bilaterally, whereas both tests failed in our case. Finally, in their case, the patient developed tetraplegia with a near locked-in state and eventually died, whereas our patient was left with only the eye-movement abnormalities.

Several other cases in the literature have some features similar to those of our case. Those cases with similar oculomotor findings or prominent alterations in consciousness are summarized in Table 1. Approximate locations of many of the cited lesions are diagrammed in Fig. 2. A diagram of the locations of relevant structures is in Fig. 3. As would be expected, the lesions with the greatest involvement of the reticular activation system correlate with the greatest alterations in consciousness. The only report in the literature featuring waxing and waning consciousness, as in our case, was that of Böttner-Ennever et al. (15). Although the course and duration of the episodes were longer than those in our case, this patient also lacked vertical pursuit and saccades. Optokinetic testing elicited no response, but oculocephalic re-
sponses were full. Pupillary responses were normal. Autopsy revealed bilateral destruction of the riMLF with preservation of the nD and inc (15).

The phenomenon of intermittent unresponsiveness has received attention in the recent literature (16-19). These reports, however, pertain to intermittent stupor of idiopathic origin. In our case, the proximity of the lesion to the mesencephalic reticular formation may clearly be implicated. It is well established that mesencephalic lesions can cause hypersomnia (20). Certainly, our case demonstrated many other signs of midbrain ischemia at varying times, such as transient right-sided weakness and pupillary abnormalities. Therefore, we propose that our patient's intermittent stupor was related to intermittent ischemia more widespread than the observed fixed lesion and involving more of the thalamomesencephalic reticular formation. This could be a result of a steal phenomenon occurring because of the hypertensive episodes, thus drawing blood away from the midbrain. In our case, the infarct involved a portion of the territory of the posterior thalamo-subthalamic paramedian artery (10,21). Perhaps a proximal stenosis of this particular vessel was a cause of this possible steal phenomenon. Alternatively, it is possible that a pressor effect of the reticular formation (20) is induced by the ischemia and that the hypertensive episodes are a result of rather than a cause of the ischemia.

Regardless of which mechanism is in operation in this case, it is worthy of report that intermittent stupor may be a logical neuroanatomical companion to focal thalamomesencephalic lesions, including the area of the riMLF, and consequently can be seen in cases of Parinaud's syndrome. This particular lesion resulted in a complete vertical gaze paralysis and intermittent stupor in the case we observed. Finally, cases such as these need not have the poor outcomes frequently reported elsewhere (4,10-12,15). Indeed, they can recover full neurologic function with the exception of their gaze abnormality.

Acknowledgment: We thank Joan Thomson for her invaluable assistance in preparing the figures for this manuscript.

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Lid Nystagmus as a Sign of Intrinsic Midbrain Disease

Michael C. Brodsky, M.D. and Frederick A. Boop, M.D.

A 6-year-old boy with signs and symptoms of ocular myasthenia gravis had lid nystagmus evoked by horizontal gaze. MR imaging demonstrated an intrinsic midbrain lesion, which was diagnosed by biopsy as a low-grade astrocytoma. In the setting of ocular myasthenia gravis, the finding of lid nystagmus may serve as a useful clinical sign of intrinsic midbrain disease.

Key Words: Lid nystagmus—Ocular myasthenia—Ophthalmoplegia—Midbrain tumor.

The terms "lid nystagmus," "upper lid jerks," and "lid hopping" have been applied to a rare neuro-ophthalmic phenomenon in which a series of rapid, rhythmic, upward jerking movements of the upper lids occur alone or in conjunction with specific movements of the eyes or head (1-14). Clinical reports suggest that this phenomenon occurs in the setting of posterior fossa disease (1). We describe a child with bilateral ptosis and diffuse ophthalmoplegia suggestive of ocular myasthenia gravis in whom the atypical finding of lid nystagmus led to the diagnosis of midbrain astrocytoma.

CASE REPORT

A healthy 6-year-old boy was referred for evaluation of gradually progressive exotropia and bilateral upper eyelid ptosis of 6 months duration. His mother stated that the ptosis was usually mild upon awakening and worse as the day progressed. There was no history of headaches, nausea or vomiting, mental status changes, decreased motor strength, or difficulty swallowing or chewing. There was no family history of ptosis or ophthalmoplegia.

Facial examination demonstrated a severe bilateral ptosis and a large exotropia (Fig. 1). Corrected visual acuity was 20/20 in each eye. The pupils were equal in size and normally reactive to light, with no afferent pupillary defect. Extraocular movements were mildly limited in all fields of gaze with a severe adduction deficit in the right eye as shown in Fig. 2. Horizontal and vertical saccades were slow in all directions. The patient was unable to converge his eyes. He had no nystagmus when he looked straight ahead in his exotropic position of gaze, but developed a gaze-evoked nystagmus in horizontal and vertical gaze. He usually fixated objects of interest with his left eye which necessitated a compensatory right face...
FIG. 1. Facial photograph demonstrating bilateral upper eyelid ptosis and exotropia.

turn and a slight chin elevation. He had 45 diopters of exotropia in all fields of gaze except for left gaze where his exotropia increased to greater than 90 diopters.

Horizontal pursuit movements or saccades in either direction evoked a large-amplitude upper lid nystagmus that lasted for the duration of horizontal gaze. Each abnormal lid movement consisted of a rapid, conjugate, upward jerk of both lids that was followed immediately by a slower downward drift to the original ptotic position. During horizontal pursuit movements, the lids jerked at a frequency of approximately one cycle per second. Careful examination of videotapes disclosed no associated vertical movement of the eyes. In sustained lateral gaze, the lid nystagmus continued as a horizontal gaze-paretic nystagmus supervened. During attempted upgaze, the lid nystagmus increased in amplitude and coincided with a large-amplitude, synchronous upbeating nystagmus. Attempted upgaze produced no visible retraction movements of the globes. During fixation of a stationary object, an occasional spontaneous upward jerk of the lids was observed. The patient had a positive Cogan’s lid twitch sign. He displayed equivocal levator fatigability; however, his ptosis improved noticeably after 30 minutes of sleep. Intramuscular injection of neostigmine 0.8 mg produced no visible change in his ptosis or ophthalmoplegia. Results of a neurological examination were otherwise normal.

A magnetic resonance (MR) scan of the head demonstrated a 2-cm mass with low signal intensity on T1-weighted images and high signal intensity on T2-weighted images within the midbrain tegmentum (Fig. 3). There was mild enlargement of the ventricular system with sparing of the fourth ventricle secondary to compression of the aqueduct of Sylvius. Results of a stereotactic biopsy revealed a low-grade astrocytoma.

The patient was treated with radiation therapy consisting of 5,400 cGy over a 6-week period. Two

FIG. 2. Versions in secondary positions of gaze demonstrating diffuse ophthalmoplegia with marked adduction lag in the right eye.
years after initial presentation, he is attending public school and appears to be functioning normally except for mild speech impairment. His parents state that his ptosis has resolved, but his exotropia persists.

DISCUSSION

Upper lid nystagmus is considered pathological when it occurs in the absence of synchronous vertical movements of the globes. Nystagmus-like jerking of the upper lids has been described in numerous pathological conditions. In each case, the abnormal lid movements have been evoked by specific movements of the eyes or head. Most previously reported cases can be subdivided into lid nystagmus evoked by convergence (Pick's sign) and lid nystagmus evoked by horizontal gaze.

Convergence-evoked lid nystagmus was first reported in 1916 by Pick (2) in a patient who had multiple sclerosis and spastic quadriparesis. The lid nystagmus was observed in primary gaze in the absence of bulbary nystagmus. The lid movements became accentuated during convergence and also upgaze, where a synchronous upbeatng nystagmus appeared. Pick (2) hypothesized that lid nystagmus may reflect abnormal excitation within the oculomotor nuclei radiating to the cell bodies that control levator function. Rohmer and colleagues (3) noted convergence-induced lid nystagmus in a patient with a posttraumatic dorsal midbrain syndrome and a left third nerve palsy. Sanders and coworkers (4) described convergence-induced lid nystagmus induced by convergence in a patient with a cerebellar sarcoma that filled the fourth ventricle. Safran and coworkers (5) described convergence-induced lid nystagmus in two patients cerebellar system disease and speculated that a phasically initiated instability of cerebellar origin might disrupt the normal physiological increase in levator tonus that occurs during convergence. As an alternative hypothesis, they suggested that convergence-evoked lid nystagmus might also represent the effect of gaze-evoked nystagmus of cerebellar origin upon the normal physiological eyelid retraction evoked by convergence. Salisachs and Lapresle (6) noted convergence-evoked lid nystagmus in patient with Miller Fisher syndrome. Howard described the same phenomenon in a patient with a pontomedullary angioma (7).

Gaze-evoked lid nystagmus was first reported in 1916 by Popper (8) in an alcoholic patient with a left-beating vestibular nystagmus. Sittig (9) and Wilbrand and Saenger (10) subsequently described gaze-evoked lid and ocular nystagmus in patients clinical signs of brainstem dysfunction without further clinical or pathological localization. Daroff and colleagues (11) described a patient with lateral medullary syndrome who had lid nystagmus that was evoked by lateral gaze and inhibited by convergence.

The fact that our patient's lid nystagmus occurred in the absence of any visible vertical move-

FIG. 3. MR images demonstrating intrinsic midbrain lesion. **Left:** T2-weighted (TR = 2500; TE = 90) axial MR image demonstrating large intrinsic hyperintense midbrain glioma. **Right:** T1-weighted (TR = 700; TE = 11) sagittal image (postgadolinium) demonstrating the rostrocaudal extent of the tumor.
ment of the globes led us to conclude that the abnormal lid movements somehow resulted from the abnormal innervational milieu created by his slowly growing tegmental tumor. In upgaze, the amplitude of the lid nystagmus increased as a large-amplitude upbeating nystagmus supervened, suggesting that the observed lid movements in upgaze were, at least in part, secondary to the ocular nystagmus.

The pathophysiology of lid nystagmus is unknown. In this case, however, its neuroanatomical substrate can clearly be localized to the midbrain tegmentum. Our patient’s neuroophthalmic findings suggest a combined disturbance of supranuclear (periodic firing of paretic levator muscles during lateral and upward pursuit movements), nuclear (bilateral upper eyelid ptosis), and possibly internuclear (selective impairment of adduction) pathways. His bilateral ptosis was similar to that described in previous reports of “midbrain ptosis,” which is attributable to a dorsal midbrain lesion involving cell bodies of neurons that bilaterally innervate the levator muscles in the central caudal nucleus (12-16). Midbrain ptosis can occur as an isolated finding or in combination with diffuse ophthalmoplegia, internuclear ophthalmoplegia, or third nerve palsy (17,18). Our patient’s slow abducting saccades suggested that descending pathways for horizontal gaze were also affected, albeit to a lesser degree (17,18).

Intracranial compressive lesions involving the brainstem and cavernous sinus can occasionally present with clinical findings indistinguishable from myasthenia gravis (19-22). Our patient had signs and symptoms of ocular myasthenia gravis (a history of minimal ptosis upon awakening with worsening as the day progressed, absence of pain, absence of pupillary involvement, and a positive Cogan’s lid twitch sign). Horizontal eye movements in myasthenia gravis are occasionally accompanied by twitching or fluttering movements of the upper lids; however, lid nystagmus is uncharacteristic of neuromuscular junction disease. The absence of levator fatigability, the presence of slow saccades with minimal limitation of ocular rotations, and the negative Prostigmine test called the diagnosis of myasthenia gravis into further question and led us to order MR imaging to rule out a mass lesion.

Ragge and Hoyt (23) recently described a similar child with neurofibromatosis and a midbrain glioma who had bilateral fatigable ptosis, diffuse ophthalmoplegia, a positive Cogan’s lid twitch sign, and a negative Tensilon test. Interestingly, their patient had unilateral “lid hopping,” which was characterized by a momentary elevation or fluttering of the phtotic eyelid as the patient visually pursued an object from one position of lateral gaze to another. The ptosis resolved following radiation therapy to the tumor. Ragge and Hoyt (23) attributed the patient’s neuro-ophthalmic signs to “midbrain myasthenia” and hypothesized that tumor infiltration within the midbrain may have critically reduced acetylcholine levels at centrally located acetylcholine synapses (most likely at the synapses between supranuclear pathways in the brainstem and the nuclear complex of the third nerve), resulting in fatigable ptosis. The similar myasthenic presentation of a midbrain tegmental tumor in our case raises the possibility that lid nystagmus may be a neuro-ophthalmic sign of “midbrain myasthenia.” Conceivably, lid nystagmus in the setting of an intrinsic midbrain lesion could require a combination of (a) an intermittent conduction block at the synaptic junction of supranuclear neurons of the posterior commissure with the central caudal nucleus (midbrain myasthenia), and (b) nuclear involvement at the level of the central caudate nucleus. Why intermittent levator activity should somehow be potentiated by horizontal gaze is unclear.

The finding of lid nystagmus in the setting of ocular myasthenia gravis may serve as a useful clinical sign of intrinsic midbrain pathology. Attention to this clinical sign may help the clinician select out those patients who have underlying central nervous system disease.

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Neuro-Ophthalmology and Systemic Disease—Part II*
An Annual Review (1994)

Nancy J. Newman, M.D.

Any disease process affecting the nervous system may have neuro-ophthalmologic manifestations and implications. This review highlights those advances in our knowledge of systemic disease of particular interest to the neuro-ophthalmologist. Many of the most important contributions of 1994 were in the areas of genetics, vascular disease, and demyelinating disease.

Kaufman (137) reviewed the recent advances in neuroimaging, especially vascular neuroimaging, and its impact on neuro-ophthalmology. Magnetic resonance angiography (MRA) continues to become more refined, more sensitive, and more specific to particular vascular abnormalities depending on the technical methods selected. In a masked study assessing the sensitivity of time-of-flight and phase-contrast MRA in the detection of intracranial aneurysms, three-dimensional time-of-flight MR was more sensitive than three-dimensional phase-contrast or standard MR imaging (138). However, although aneurysms as small as 3 mm could be detected, 5 mm appeared to be the critical size, with time-of-flight MRA providing a sensitivity of 87.5%. Combinations of multiple modalities would certainly increase sensitivity. However, aneurysms less than 5 mm in size can rupture, making conventional arteriography still essential in the patient under high suspicion for aneurysm, especially multiple aneurysms (139,140). Certainly in the acute-care setting, where sophisticated MR imaging may not be available, arteriography is indicated in the patient with a pupil-involving third-nerve palsy. Walter et al. (141) described two patients with oculomotor nerve palsies precipitated by minor head trauma with negative CT scans, who were subsequently discovered to have ipsilateral posterior communicating artery aneurysms. Intracranial aneurysm must be added to the list of occult mass lesions causing third-nerve palsies in the setting of minor trauma. Giant cerebral aneurysms arising from the intracranial internal carotid artery and its branches can produce progressive visual loss from compression of the anterior visual pathways (142). When conventional neurosurgical intervention with clipping or trapping of the aneurysm is not feasible, percutaneous intraarterial embolization with detachable balloons or electrocoils may provide an alternative therapy. Vision may stabilize or improve and the patient may be protected against subsequent hemorrhage. Although complications of endovascular techniques are significant, coils may be preferable to balloons.

Neurologic complications of cerebral angiography using transfemoral catheterization were examined in 1,000 consecutive procedures on patients ranging in age from 1 month to 96 years (average age 53 years) at a major teaching institute (143). The neurologic complication rate was 1% overall and 0.5% for persistent deficits. All events occurred in patients being evaluated for stroke, transient ischemic attack, or carotid bruit, and a higher age, longer procedure time, and greater volume of radiographic contrast was noted in these patients than in the study population. In his editorial commentary, Gabrielsen (144) warns that most of our arteriography patients now fit into this high-risk group and not all institutions will have such favorable complication rates. However, he stresses the
continued importance of appropriately performed cerebral angiography in the course of modern clinical management. Ocular complications may occur during performance of the Wada test (145), including a possible toxic reaction to sodium amobarbital with choroidal infarctions. Complications may also arise during carotid balloon occlusion testing, including transient monocular visual loss (146) and transient ocular ischemic syndrome (147). The latter manifested as orbital pain and visual blurring and was likely related to too rapid infusion of saline distal to a double-lumen balloon into the ophthalmic artery.

In a section devoted to vascular disease, mention must be made of a remarkable report in the New England Journal of Medicine in which an unexpected episode of classic migraine was captured during a series of blood-flow measurements with positron-emission tomography (PET) (148). Despite no clinically reported aura aside from a brief difficulty focusing clearly, PET images demonstrated bilateral hypoperfusion beginning in the occipital lobes and spreading anteriorly into the temporal and parietal lobes. Interestingly, the cerebral blood-flow abnormalities originated bilaterally in the visual association areas, not in the primary visual cortex. The authors and the subsequent editorial concluded that the spread of flow reduction was most consistent with the spreading depression of Leao (148,149).

Demyelinating Disease

The literature in 1994 included many contributions concerning the epidemiology, genetics, imaging, and management of multiple sclerosis (MS). Two collections of articles, both supplements to volume 36 of the Annals of Neurology, are worth singling out as valuable references (150,151). Supplement 1 provides a general overview of MS based on contributions to a symposium held in September 1993. Multiple contributors well known to the MS academic community reviewed the epidemiology, natural history, genetics, and factors associated with risk or exacerbation of the disease. Basic science is reviewed, especially as regards what is known about the immunology of MS. A large section is devoted to the use of clinical trials for treatment of the disease, the techniques of clinical definition, design strategies, the role of magnetic resonance imaging in such trials, and the most promising therapies at that time, i.e., interferon-β, copolymer-1, and aminopyridines. Future prospects are discussed, including those that take advantage of recent basic science advances in our understanding of growth factors and remyelination. Supplement 2 is more specialized and reflects the reviews and recommendations of a workshop on the epidemiology and genetics of MS held in June 1993.

Individual articles concerning MS include a report on the very rare diagnosis of MS among native blacks in South Africa and Zimbabwe (152). Twelve patients are reported, six of whom became severely visually impaired from optic neuritis. The authors claim that MS in this group of patients resembles more closely the disease as reported among Asians than among white people in Africa or black individuals living in North America. In 1993, a report from the Mayo Clinic showed no association of head injury or spinal disc surgery with the onset, exacerbation, or final disability of MS (153). In a subsequent letter to the editor, the same group reported no association of cervical radiculopathy or its surgery with MS (154). Jellinek (155) reviewed the controversy regarding trauma and exacerbation of MS and proposed there still may be a role for direct central nervous system trauma as a trigger of aggravation of the disease. Retrospective studies have suggested that MS may be exacerbated in the postpartum period. In a prospective study of 53 women with a total of 69 pregnancies, Sadovnick et al. (156) found that neither pregnancy nor the six-month period after delivery was a risk factor for relapse in MS. Similarly, in a five-year prospective study of 29 women, Stenager et al. (157) reported no influence of pregnancy or childbirth on the long-term prognosis for MS. Because female patients with MS are at risk for osteoporosis secondary to gender, immobility, and corticosteroid use, Nieves et al. (158) investigated bone mineral density, vitamin D dietary intake, and vitamin D levels in women with MS. They noted significant reductions in bone mineral density, suggesting an increased fracture risk of up to threefold and a high prevalence of vitamin D deficiency; they recommended that vitamin D supplementation be instituted in female patients with MS. The possible association of MS and intracranial hypertension was discussed in an article reporting three women with both diseases, although causation remains unclear (159). A multiple sclerosis-like illness was noted in a patient with deafness and pigmentary retinopathy consistent with Usher's syndrome (160). Movement disorders in MS are unusual. Barton et al. (161) described a 59-year-old man with MS, limb and head chorea, torticollis, blepharospasm, and involuntary ocular deviations, the last most reminiscent of oculogyric crises but continuous while awake.
As regards the most common neuro-ophthalmic manifestation of demyelinating disease, optic neuritis was the topic of some notable publications in 1994. The Optic Neuritis Treatment Trial (ONTT) continues to provide important follow-up information on its cohort of patients. The visual fields were followed longitudinally and the one-year results showed that although visual fields for the majority of patients tended to return to normal (55.9% at one year), new and different patterns of defects developed, including subclinical involvement of the fellow eye (162). Furthermore, chiasmal and retrochiasmal defects occurred more commonly than previously clinically identified (13.2% of patients), and those exhibiting retrochiasmal defects were more likely to have had abnormal brain magnetic resonance imaging (MRI) at baseline than other ONTT patients. The course of visual recovery after optic neuritis was noted to be rapid, regardless of treatment with oral prednisone, intravenous methylprednisolone, or oral placebo, improvement beginning within the first two weeks in most patients and within the first month in nearly all patients (163). Baseline visual acuity was the only valuable predictor of six-month visual acuity outcome, although visual recovery was still good in most patients, even those with no light-perception vision. Therefore, patients who do not follow such a pattern of visual recovery, or those who worsen after termination of steroids, should be considered atypical and subjected to further diagnostic investigation. In a letter to the editor, Coyle (164) questioned whether the ONTT results are just as valid for men as they are for women, and whether the use of an expensive test like MRI is truly justified. In his reply, Beck (165) pointed out that the previously reported gender predilection of more women than men with optic neuritis developing MS has not been confirmed during the two-year follow-up in the ONTT or in a recent five-year prospective study. He also noted that the difference in prognosis for MS between those first-time optic neuritis patients with MRI lesions and those without is significant enough to justify obtaining MRIs at baseline. In a prospective study of 60 patients with optic neuritis without MS, 69% had oligoclonal bands in the cerebrospinal fluid and 53% had at least three white-matter lesions on MRI, and these findings were strongly correlated (166). At a mean follow-up of two years, 17 patients had clinically definite MS, 16 of whom had oligoclonal bands and 12 of whom had abnormal MRIs at presentation. In a study of patients with acute optic neuritis both with and without MS, Sellebjerg et al. (167) demonstrated that antiproteolipid protein antibodies in the cerebrospinal fluid were a more specific finding for demyelinating disease than anti-myelin basic protein antibodies and that the former may arise as a consequence of the demyelinating process.

The role of MRI in the detection and diagnosis of MS, in the prediction of disease expression and progression, and in the monitoring of treatment was the subject of several reviews and original articles in 1994. In a review of the use of brain MRI in MS, Goodkin et al. (168) discuss the importance of MRI in MS diagnosis, the difficulty with specificity for the diagnosis, especially in older patients, and the pathological correlates of these white-matter lesions on MRI. They review the correlation of lesions on MRI with traditional measures of neurologic impairment, with neuropsychologic measures, and with immune function and show how MRI, unenhanced and enhanced, has been used to follow serially patients with MS. An extension of this application is the use of MRI to monitor the response to various treatments of MS, and the authors conclude that it is important to include serial brain MRI scans as secondary or possibly primary outcome measures in future clinical trials of MS. Important questions posed include: How predictive is brain MRI when the patient presents with the first neurologic event? Does the rate of new or enhancing lesion accrual predict the clinical course? What are the optimal techniques for quantifying lesion burden? What is the optimal frequency of obtaining MRIs in MS patients? Can changes in MRI lesion burden be used as a primary outcome in treatment trials? Can different MRI techniques allow us to learn more about the active pathologic processes within the MS brain?

The impact of MRI, CT, cerebrospinal fluid (CSF) analysis, and evoked potential testing on the clinical diagnosis of MS was evaluated in 62 patients with possible or probable MS (169). Magnetic resonance imaging was crucial for diagnosis in 44% of cases, and in these cases the results of other tests did not contribute. In the remaining 56% of cases, further laboratory testing led to a diagnosis in only an additional 13% of patients. Khoury et al. (170) followed 18 MS patients clinically and with unenhanced and enhanced MRIs for one year. Positive correlations were demonstrated between accumulation of new lesions and cumulative disability, and between the number of lesions, both enhanced and unenhanced, and increasing disability. The study confirmed that new lesions may appear at times of clinical stability. Filippi et al. (171) performed quantitative brain MRIs over five years in 84 patients presenting with
clinically isolated syndromes suggestive of MS (40 with optic neuritis). Those who developed MS during follow-up (45%) had a higher lesion load at presentation than those who did not, and increasing initial lesion load correlated with a decreasing time to development of MS clinically. Confirmation that new and enlarging lesions, as well as enhancing lesions, appear less often in MS patients with benign disease was provided in a study of two groups of 11 MS patients, one group with early relapsing–remitting MS, the other with long-duration benign disease (172).

Husted (173) reviews refinements in MRI techniques that may provide increased sensitivity and specificity in the diagnosis and understanding of MS. Gadolinium enhancement helps to distinguish acute from chronic lesions, and the number and area of enhanced lesions has been correlated with clinical worsening. Fluid-attenuated inversion recovery (FLAIR) improves the detection of MS lesions in the spinal cord and brainstem. Magnetization transfer imaging, in combination with enhancement, further increases lesion contrast and increases the pathological specificity of MRI. Gass et al. (174) found that this technique could indicate the degree of demyelination and axonal loss, and proposed its use in monitoring treatment-induced changes in tissue structure. Magnetic resonance spectroscopy and magnetic resonance spectroscopic imaging may help elucidate the underlying biochemical mechanism of demyelination in MS (175,176). Progressive accumulation of neuronal damage as demonstrated by these more sensitive techniques may correlate with progressive disability better than conventional MRI (175). Normal-appearing white matter on the MRIs of MS patients may be biochemically abnormal (176).

The use of MRI findings to predict clinical outcome and the role of MRI in therapeutic clinical trials of MS were reviewed by McDonald et al. (177) in light of the conclusions of the beta-interferon-β trial. Although therapy with interferon-β1b significantly reduced the frequency of relapse and of new pathological activity as determined by MRI, no differences were noted between treated and untreated groups in the rate of clinical deterioration. This may have been a result of the relatively crude methods we have for measuring disability, combined with the variability of the course of MS and the relatively short duration of follow-up in the trial. The use of a variety of new MRI techniques (see above) has shown that the frequency of new disease activity, the total extent of abnormality, and the pathologic characteristics of the lesions can indeed predict subsequent disability in MS. It remains to be seen whether a correlation will ultimately be established between MRI findings and long-term disability in treatment trials.

Regarding treatment, Jacobs and Johnson (178) review the history of the use of interferons as treatment for MS, their biological effects, and the rationale for their use in MS and possible mechanisms of action. Interferon-β administered intrathecally or systemically significantly reduces MS exacerbations. A practice advisory from the American Academy of Neurology (179) recommended that subcutaneous human interferon-β can be used in relapsing–remitting ambulatory MS patients between the ages of 18 and 50 years who have had at least two acute relapses in the prior two years, who have no other serious concurrent illnesses, and who are not planning pregnancy. Patients older than 50 years, with more disability, or with relapsing–progressive disease might be helped. There is no evidence to suggest the medication would be helpful in primary chronic progressive patients. Preliminary results from a trial using weekly intramuscular recombinant low-dose interferon-β1b in the treatment of relapsing–remitting MS are also promising (180). In contrast to interferon-β, interferon-γ provokes exacerbations of MS. Although previous studies of interferon-α in MS have shown only equivocal results (178), a recent randomized, double-blind, placebo-controlled pilot trial of intramuscular high-dose recombinant interferon-α2a in 20 relapsing–remitting MS patients demonstrated reduced clinical and MRI signs of disease activity with treatment (181).

Preliminary results have been released regarding the use of copolymer-1 in the treatment of relapsing–remitting MS (180). Copolymer-1 is a synthetic polypeptide that presumably works either by producing antigen-suppressor cells specific for myelin basic protein or by interfering with T-cell activation by competing with myelin basic protein or by interfering with T-cell activation by competing with myelin basic protein for major histocompatibility complex binding sites responsible for antigen presentation. Its daily use subcutaneously decreased the relapse rate by 24% and also decreased subsequent neurologic disability. Results of a randomized trial of 4-aminopyridine in the treatment of the symptoms of residual deficits in MS patients were in general positive, but there were significant toxic effects of treatment (182). Early studies are underway in the use of chimeric monoclonal antibodies against the CD4 antigen found on helper/inducer T lymphocytes in the treatment of MS patients (183). The treatment was effective in reducing the number of CD4 lym-
phocytes, and there were no limiting side effects, but it is too early to assess clinical efficacy. The debate continues over whether intermittent intravenous cyclophosphamide therapy is beneficial in the treatment of MS, especially those patients with rapidly progressive disease (184,185). At the root of the controversy is the need for well-designed randomized, controlled trials. Given how commonly patients with MS are treated with glucocorticoids and ACTH, a recent report on the use of glucocorticoids in rats with experimental allergic encephalomyelitis (EAE) is of interest (186). Continuous steroid treatment completely blocked EAE, but sudden withdrawal of steroids made the animals worse than control animals who had received no treatment at all. The authors conclude that abrupt discontinuation of steroids provokes inflammatory brain disease; gradual reduction of steroid therapy in inflammatory neurologic disease would appear prudent.

Parainfectious encephalomyelitis may cause optic neuritis and visual loss, as well as other central nervous system signs, some of which may be related to raised intracranial pressure (187). Medical therapy with steroids may be helpful in treatment of the disease, although relapses, as with EAE, may occur with steroid withdrawal. Surgical shunting or decompression procedures may prove necessary if medical therapy fails and there is ongoing elevated intracranial pressure. Devic’s disease, neuromyelitis optica, manifested by acute or subacute optic neuropathy and myelopathy, is considered by some to be a form of MS, by others a distinct nosological entity. Fazekas et al. (188) describe two women with Devic’s and MRI findings restricted over several years entirely to the optic nerves, chiasm, and spinal cord, offering further support that this is a clinical entity separate from typical MS. An autosomal dominant, adult-onset leukodystrophy was described in a kindred whose symptomatic members suffered progressive, prominently cerebellar and pyramidal dysfunction similar to chronic progressive MS (189).

Demyelination of peripheral nerves and roots is generally believed to underlie that form of Guillain-Barre syndrome designated Miller Fisher syndrome (MFS) and clinically characterized by ophthalmoplegia, ataxia, and areflexia. Debate continues regarding the contribution of occasionally demonstrated central nervous system lesions to the clinical expression of this syndrome. Najim Al-Din et al. (190) reviewed the neuro-ophthalmic manifestations of 20 of their patients with MFS and concluded that the symmetrical nature of the ophthalmoplegia and ataxia, combined with apparent supranuclear, nuclear, and internuclear signs, favors centrally placed lesions. The same group of authors then reviewed 109 reports in the literature on MFS, representing 243 patients (191). They noted that most cases had symmetrical failure of upgaze followed by loss of lateral gaze and then downgaze, with recovery in the opposite pattern. Fifty-eight patients were reported with sparing of downgaze and 192 patients (79%) had relative sparing of the eyelids. Lid retraction, preserved Bell’s phenomenon despite upgaze paralysis, and other findings suggesting supranuclear localization were also described. The authors concluded that MFS represents a brainstem syndrome rather than an unusual variant of the Guillain-Barre syndrome. A supporter of MFS as a variant of demyelinating polyneuropathy, Ropper (192) proposes four syndromes of acute regional weakness, with clinical, spinal fluid, and electrophysiologic similarities to typical Guillain-Barre syndrome, as a spectrum of disease among the acute immune polyneuropathies: lumbar polyradiculopathy, facial diplegia and distal limb paresthesias, sixth-nerve paresis and distal limb paresthesias, and ophthalmoplegia with pharyngeal–cervical–brachial weakness and ataxia. A 65-year-old man with only mild ophthalmoplegia had MFS with prominent bulbar symptoms (193). He had high titers of GQ1b-ganglioside antibodies, previously noted to be strongly associated with MFS. A 17-year-old patient with known systemic lupus erythematosus developed severe MFS (194). Treatment with immunoglobulins, steroids, and cyclophosphamide failed, but she had dramatic clinical improvement immediately following plasma exchange, suggesting the presence of a circulating neurotoxic factor.

AIDS

The number of individuals testing positive for the human immunodeficiency virus (HIV) and the number of persons diagnosed with acquired immunodeficiency syndrome (AIDS) continues to rise. Particularly rapid is the increase in the number of reported cases of heterosexually acquired AIDS (195). Persons at highest risk include adolescents and adults with multiple sex partners, those with sexually transmitted diseases, and heterosexually active persons residing in areas with a high prevalence of HIV infection among intravenous drug users. In a study of survival and disease progression according to gender of patients with HIV, HIV-infected women were at increased risk of death and bacterial pneumonia (196). This may re-
fect differential access to health care and standard treatments or different socioeconomic status for women compared with men with HIV.

AIDS-associated neurologic conditions affect 40-60% of AIDS patients, are the presenting symptom of AIDS in 5-10%, and are identified pathologically in over 90%. In a multicenter AIDS cohort study of primarily highly educated homosexual and bisexual HIV-positive men over the years 1985-1992 (197), the overall incidence rates of all HIV-related neurologic diseases, with the exception of HIV dementia, showed upward trends. There was a protective trend of antimicrobial prophylaxis on toxoplasmosis and cryptococcal meningitis, but use of antiretrovirus agents was not protective against HIV dementia. As more people with profound immunosuppression live longer, the overall incidence of HIV-related neurologic diseases can be expected to rise. The HIV p24 antigen, a putative marker of virus load, was detected more frequently in the cerebrospinal fluid and blood of HIV patients with significant HIV-related dementia, and the antigen concentration correlated directly with the degree of cognitive impairment, suggesting that the p24 antigen may be a useful marker for HIV dementia (198). Disturbances of postural control, as measured by standard static posturography and postural reflexes, were demonstrated to be one of the earliest neurological abnormalities in patients with early HIV dementia (199).

Neuro-ophthalmologically, three cases were reported of AIDS-related non-Hodgkin's lymphoma involving the orbit: in one case a Burkitt's-type in one orbit with concurrent widespread abdominal involvement (200), in the second case presenting simultaneously in both orbits (201), and in the third case presenting simultaneously in the ipsilateral eye and orbit (202). In another report, a 44-year-old HIV-positive man presented with bilateral uveitis and myelitis, for which no opportunistic infectious cause other than the HIV itself could be found (203). Symptoms and signs improved with only oral zidovudine and topical ocular steroids, suggesting primary HIV infection of the spinal cord and eye. Balint's syndrome was produced by bilateral parieto-occipital lesions, confirmed histopathologically to be caused by progressive multifocal leukoencephalopathy (PML) (204).

AIDS-related PML was the cause of a bizarre movement disorder, beginning with motor awkwardness, progressing through generalized motor slowness to dystonic movements and ultimately generalized myoclonus (205). Although PML was demonstrated pathologically, especially involving the subcortical U fibers, MRI performed two months after symptom onset and five months prior to death was normal. Cytomegalovirus was determined to be the cause of a severe multifocal neuropathy in 15 patients in the late stages of HIV infection (206). Detection of cytomegalovirus DNA by PCR in the cerebrospinal fluid was useful. Fourteen of 15 patients improved after treatment with ganciclovir or foscarnet. The incidence of tuberculosis has increased in recent years, at least in part as a result of AIDS, and outbreaks of multidrug-resistant organisms has heightened concern (207).

In an excellent review of the recent developments regarding tuberculosis, especially in the AIDS patient, Haas and Des Prez (207), discussed how the manifestations of tuberculosis in AIDS patients are influenced by the degree of immunosuppression. The authors stressed that patients with AIDS and pulmonary tuberculosis are highly contagious but that appropriate infection control and complete courses of multiple drug therapy are effective. Horowitz et al. (208) described the case of a 29-year-old HIV-positive man with cerebral syphilitic gumma diagnostically confirmed by silver-impregnation staining, immunofluorescence, and the polymerase chain reaction on autopsy tissue. It has been suggested that patients with HIV infection are at greater risk of acquiring neurosyphilis, that neurosyphilis in HIV-coinfected patients follows a more aggressive or atypical course, that serologic tests for syphilis may be falsely negative in the presence of HIV coinfection, and that syphilis in the HIV patient may respond differently to antibiotic treatment. Gordon et al. (209) showed that in HIV patients with early syphilis, therapy with intravenous penicillin G for 10 days may fail, and neurosyphilis may develop. In a most remarkable editorial, Simon (210) readdressed the issues of neurosyphilis in the HIV patient and concluded that there is no hard evidence to support the contention that syphilis is an opportunistic infection in HIV-coinfected patients or that it is more aggressive, clinically atypical, or more refractory to treatment. Serum antibodies to Rochalimaea henselae, the pathogen associated with cat-scratch disease, were found more frequently among HIV-positive patients with neurologic disease than those without, suggesting the possibility that some AIDS-related encephalopathies may be due to central nervous system invasion by this organism (211). Further corroborative studies are necessary.

Primary central nervous system lymphoma (PCNSL) arises in 1.5-5% of AIDS patients and conventional therapy with steroids and cranial radiation provides a median survival of only two to...
five months (212). Compared to PCNSL in immunocompetent patients, PCNSL in AIDS patients is more likely to be multifocal, to involve the meninges, to be ring-enhancing, and to hemorrhage. Forsyth et al. (212) treated 10 AIDS patients with PCNSL with chemotherapy in addition to radiation therapy; although there was a response to chemotherapy, only two patients survived for one year or longer.

To determine whether sociodemographic characteristics of HIV patients influence the use of prophylactic drug therapy, Moore et al. (213) studied 838 patients and found that blacks were significantly less likely than whites to have received antiretroviral therapy or Pneumocystis prophylaxis when first referred to an HIV clinic. This disparity suggests a need for interventions to ensure uniform access to treatment and uniform standards of care. In a comparison of the long-term prognosis of patients with AIDS treated and not treated with zidovudine, the death rate within the first year since starting treatment was markedly lower among the treated patients, but after two years the beneficial effect had disappeared (214). Furthermore, for asymptomatic patients treated with 500 mg of daily zidovudine, a reduction in the quality of life due to severe side effects of therapy approximately equals the increase in the quality of life associated with delay in the progression of HIV disease (215). Although reverse transcriptase inhibitors such as zidovudine are effective in the treatment of acute infection of target cells, they have no effect on chronically infected cells (216). Furthermore, resistance of HIV to zidovudine has been documented to occur. For patients with HIV infection who cannot tolerate or have not responded to zidovudine, zalcitabine and didanosine are equally efficacious in delaying disease progression and death (217). However, patients with advanced disease appear to have a clinical course that may not be markedly altered by any of the currently available nucleoside analogs used as monotherapy. New therapies are needed and investigations continue regarding combination therapy with nucleoside and nonnucleoside reverse-transcription inhibitors (218), protease inhibitors (218), vaccines (219,220) and gene therapy (221).

INFECTIOUS DISEASE

Advances in diagnostic molecular microbiology have revolutionized the identification of infectious agents, including bacteria, mycobacteria, fungi, and viruses that either are fastidious and grow slowly or cannot be cultured (222). These techniques have shortened the time necessary to identify fastidious microorganisms, expanded the number of identifiable human pathogens, and improved the accuracy of subtyping of pathogens. The two principal molecular techniques are nucleic acid hybridization with a specific DNA or RNA probe and DNA amplification by the polymerase chain reaction (PCR) (222). These techniques have provided further insight into Rochalimaea henselae infection, a presumed zoonosis, with the domestic cat, via its fleas, as the major persistent reservoir (223-225). The microorganisms are small gram-negative rods, classically assigned to the Rickettsiaceae, although recent evidence favors reclassification among the Bartonellaceae (225). The most common manifestation in humans is cat-scratch disease, a persistent necrotizing inflammation of the lymph nodes, which is estimated to affect 22,000 people in the United States annually (223). In the immunocompromised patient, such as those with AIDS, these gram-negative bacteria may cause bacillary angiomatosis, a potentially lethal vascular proliferative response to the organism in skin, bone, or other organs. Lee et al. (226) reported on a 70-year-old immunocompetent man with bacillary angiomatosis of the conjunctiva, and Le et al. (227) used a conjunctival swab and PCR to identify Rochalimaea henselae as the causative organism of a conjunctival nodule in an HIV-positive man who had recently acquired a kitten. Golnik et al. (228) described four patients with intraocular inflammation, visual loss, white retinal lesions, macular eduate, and optic nerve head swelling, all with elevated serum antibody titers to Rochalimaea henselae and Rochalimaea quintana. Improvement occurred after treatment with oral ciprofloxacin hydrochloride and prednisone or doxycycline hyclate, but the natural history of ophthalmic manifestations of this disease remains unknown. The authors concluded that lack of a history of previous cat scratches or lymphadenopathy does not preclude the presence of Rochalimaea infection; that patients with vitritis, retinitis, neuroretinitis, or optic perineuritis of unknown etiology should be investigated for Rochalimaea; and that antibiotics afford the best chance for maximal visual recovery. It remains unclear whether efforts at the public health level should be instituted, including treatment or vaccination of cats and flea control (225, 229).

Lyme disease, the result of infection with the spirochete Borrelia burgdorferi, may cause long-term complications, including persistent arthralgias, extremity numbness, fatigue, poor concentration.
and memory loss, emotional lability, and difficulty sleeping (230). Delayed initial treatment is the principal risk factor for continued residual symptoms. Bergdoff et al. (231) reviewed the ophthalmic manifestations of Lyme borreliosis, including uveitis, optic neuritis, and ocular motor nerve palsies. Although this contribution offers a much-needed review of the European literature on this subject, the ocular manifestations included are protean, and may be overly inclusive. As with other spirochetal infections, antibiotic treatment of Lyme disease may cause a Jarish-Herxheimer reaction with transient exacerbation of existing lesions, in one case worsening of presumed Lyme optic neuropathy (232). One patient with Lyme disease developed an isolated fascicular sixth-nerve palsy after a one-month course of oral antibiotics (233). Symptoms persisted with intravenous antibiotics but resolved with corticosteroid therapy.

In an excellent editorial, Tyler (234) discussed the use of PCR as a sensitive and rapid technique in the diagnosis of viral central nervous system disease. The use of PCR on cerebrospinal fluid samples has allowed for diagnosis of herpes simplex virus (HSV) encephalitis, obviating the need for brain biopsy. The technique has also been used in the detection and diagnosis of Epstein-Barr virus, varicella-zoster virus, and cytomegalovirus infection. PCR may prove useful in quantifying HIV load and in identifying the JC virus in presumed PML. However, the identification of viral DNA in the central nervous system by PCR does not assign a viral etiology to a disease. Baringer and Pisani (235) analyzed brain samples from individuals dying of nonneurological disease and detected HSV genomic sequences in 26 (65%) of 40 trigeminal ganglia samples and in 14 (35%) of 40 brains, especially in the medulla, olfactory bulbs, pons, gyri rectus, amygdala, and hippocampus. This suggests that the virus may exist in the latent state in normal central nervous system. The treatment of acute symptomatic herpes zoster infection is controversial. In a double-blind, controlled trial, treatment with acyclovir for 21 days or the addition of oral prednisolone to acyclovir therapy conferred only slight benefits over standard seven-day treatment with acyclovir, and neither additional treatment reduced the frequency of postherpetic neuralgia (236).

An infection also of interest to neuro-ophthalmologists is Whipple’s disease, the small gram-positive bacillus Tropheryma whippelii, in the peripheral blood of two patients with Whipple’s disease. This identified the Whipple’s bacillus as a red-cell-associated organism and demonstrated that the disease can be diagnosed on peripheral blood samples without tissue biopsy. Another infection of great neuro-ophthalmic importance is rhino-orbital-cerebral mucormycosis. Yohai et al. (238) extensively reviewed mucormycosis, a highly aggressive, frequently fatal, fungal infection most commonly found in diabetic and immunocompromised patients. Factors related to lower survival include delayed diagnosis and treatment, hemiparesis, bilateral sinus involvement, leukemia, renal disease, treatment with deferoximine, and possibly facial necrosis. Standard treatment consists of amphotericin B and aggressive surgery, with possible adjunctive therapies including local amphotericin B irrigation, hyperbaric oxygen, and optimization of immunosuppressive regimens in transplant patients. Cystercerosis causes cerebral lesions that commonly result in seizures, headaches, and frequently hydrocephalus (239). Neuro-ophthalmic manifestations may reflect raised intracranial pressure or mass lesions within the cerebral parenchyma. The disease should be considered in those patients with tapeworms, exposure to those with tapeworms, or exposure to endemic areas.

TUMORS AND PARANEOPLASTIC SYNDROMES

Pollack (240) reviewed brain tumors in children, the largest group of solid neoplasms in children, second only to leukemia in their overall frequency. Specific tumors given particular attention included low- and high-grade gliomas, medulloblastomas, brainstem gliomas, ependymomas, and craniopharyngiomas. Brain tumors in children range from the very benign to the highly malignant. Age-related factors in the vulnerability of the brain to the various toxic and therapeutic effects of different therapies make management difficult. Continued enrollment of children with brain tumors in multicenter trials is essential for the development of appropriate interventions. Among children with medulloblastoma, surveillance scanning is probably of little clinical value, as scanning detected a minority of recurrences and no patient who had a recurrence survived (241). Weiner et al. (242) retrospectively analyzed the pathologic and clinical characteristics of 56 patients with craniopharyngioma and concluded that squamous papillary cran-
iopharyngiomas, like adamantinomatous tumors, may recur when subtotally resected, that the most significant factor associated with recurrence is the extent of surgical resection rather than histopathological subtype, that brain invasion in totally resected tumors does not predict higher recurrence, and that gross total resection is associated with a significantly lower recurrence rate and can be achieved without sacrificing functional outcome. During pregnancy, pituitary adenomas may grow and vision may be at risk, especially if bromocriptine has been discontinued. Kupersmith et al. (243) studied 65 women with previously untreated pituitary tumors and noted visual loss during pregnancy in six of the eight patients with macroadenomas but none of the 57 patients with microadenomas.

Gliomas of the anterior visual pathways account for less than 5% of all brain tumors in children, but up to 70% of children with optic pathway tumors have neurofibromatosis type 1 (NF1). In a study of 176 children with NF1 and neuroimaging, Listernick et al. (244) found tumors of the anterior visual pathways in 15% of asymptomatic children with NF1. Rapidly progressive tumors usually presented during the first six years of life and subsequent tumor progression was uncommon. The authors concluded that screening neuroimaging in asymptomatic children with NF1 has limited utility, but that periodic screening ophthalmic examinations are important. Ophthalmic manifestations of neurofibromatosis type 2 (NF2) include cataracts, retinal hamartomas, and epiretinal membranes. In a study of 63 affected individuals from 32 NF2 families (245), ocular symptoms were the presenting features in 12.7% of cases, while symptoms from vestibular schwannomas, other central nervous system tumors, and skin tumors were the initial features in 44.4%, 22.2%, and 12.7% of patients, respectively. On examination, however, cataracts were noted in 81% of patients. In addition to different chromosomal loci for the abnormal genes in NF1 and NF2 (chromosome 17 for NF1; chromosome 22 for NF2), the two disorders have little phenotypic overlap.

The paraneoplastic syndromes reflect the remote effects of systemic cancers and frequently involve the central and peripheral nervous systems. As more clinical syndromes are defined and more antibodies associated with the syndromes are characterized, attempts are being made to organize and classify the increasingly complex array of syndromes and antigen–antibody interactions (246–248). Thirkill (249) provided an extensive review of the most common ocular paraneoplastic syndrome, cancer associated retinopathy, or CAR syndrome. Two articles appearing in Ophthalmology address the paraneoplastic retinopathy associated with cutaneous malignant melanoma, or MAR syndrome (250,251). Kim et al. (250) reported on three men with melanoma-associated retinopathy who presented with flickering black and white spots, shimmering patches of colors, and night blindness that was acute and nonprogressive. They confirmed that the flash electroretinographic b-wave was diminished, similar to the pattern seen in congenital stationary night blindness. Weinstein et al. (251) confirmed the presence of high-titer immunoglobulins reactive only with a subset of retinal bipolar cells in MAR syndrome. Harris et al. (252) proposed that a patient with non-Hodgkin’s lymphoma suffered bilateral orbital myositis, cranial neuropathies, and a sensory polyneuropathy as a paraneoplastic syndrome. Extracocular muscle biopsy revealed granulomatous inflammation without neoplastic invasion, and the cranial neuropathies and myositis improved with immuno­suppressive therapy even as the patient’s underlying neoplasia progressed.

Some neurologic paraneoplastic antibodies have been characterized based on antibody–antigen specificity and have been linked to particular paraneoplastic syndromes that are associated more commonly with certain systemic tumor types (247). The anti-Hu antibodies occur most frequently with small cell lung cancer and are associated with clinical syndromes of encephalomyelitis, sensory neuropathy, and autonomic neuropathy (253). The anti-Yo antibodies are seen most commonly with ovarian and breast cancer and typically are associated with cerebellar degeneration (247). Anti-Ri antibodies also occur most frequently in those patients with breast cancer and ocular movement disorders, particularly opsoclonus, commonly accompanied by axial ataxia (247). However, overlap of clinical syndromes is not uncommon, unusual tumors may underlie the syndromes, otherwise clinically classic antibody-negative cases can occur, and the antibodies may be present in patients with neoplasms but no paraneoplastic syndrome. Hersh et al. (254) found anti-Hu antibodies in a patient with small cell lung cancer and opsoclonus, myoclonus, ataxia, and encephalopathy. Verschuuren et al. (255) found anti-Hu antibodies in a patient with sensory and autonomic neuropathy and a metastatic chondrosarcoma that expressed Hu antigens. This patient’s paraneoplastic syndrome improved after surgical treatment of the tumor and immunosuppressive treatment, including plasmapheresis. Five patients
were described in whom paraneoplastic sensory neuropathy was stable or only slowly progressive over time, despite high titers of anti-Hu antibodies (256). Casado et al. (257) reported on a 57-year-old woman with opsoclonus, myoclonus, ataxia, encephalomyelitis, and positive anti-Ri antibodies, in whom no underlying malignancy could be found. A similar case of a 73-year-old woman with progressive ataxia, opsoclonus, dementia, peripheral neuropathy, and high titers of anti-Ri antibodies came to autopsy, where no tumor was found (258). Anti-Ri reactivity was identified in immunoblots of all regions of the brain, predominantly the pons and dorsal midbrain, supporting an autoimmune antibody-mediated mechanism for the disorder. Ahern et al. (259) reported on a 38-year-old patient with temporal lobe seizures and an isolated amnestic syndrome occurring three years prior to the discovery of a testicular tumor. A serum autoantibody demonstrated an affinity for the nucleolus of cerebral cortical neurons, an antigen different from previously identified paraneoplastic neurologic antigens Hu, Yo, and Ri.

**MISCELLANEOUS**

Organ transplantation has become more common, and with it numerous complications, many of which involve the nervous system (260). Depending on the type of organ transplanted, neurologic problems are reported in 30-60% of transplant recipients. The neurologic complications may be specifically related to transplant type, but more commonly reflect the necessary immunosuppression, i.e., neurotoxic side effects from immunosuppressive drugs, infections, and the development of malignancies. As with the vitreoretinal complications of bone marrow transplantation (261), the neuro-ophthalmic manifestations may reflect direct neurotoxicity of immunosuppressive agents, infections, new lymphoproliferative disorders, or complications of the transplant procedure. Of particular neuro-ophthalmic interest is the leukoencephalopathy that occurs with cyclosporine therapy, which can cause reversible cerebral blindness. A more recently introduced immunosuppressive agent is tacrolimus (FK 506), which appears to have equal efficacy with cyclosporine in terms of patient and graft survival, but may have more adverse side effects, including neurotoxicity (262).

Obviously an important disease to neuroophthalmologists, myasthenia gravis is the subject of two comprehensive and extremely valuable reviews (263,264). Drachman (263) reviewed the diagnosis and practical management of the disease, as well as the newer developments regarding pathogenesis, immunology, and molecular biology. Weinberg et al. (264) extensively reviewed ocular myasthenia, with extraordinarily comprehensive referencing. Historical background, pathophysiology, immunogenetics, diagnostic testing, treatment options, and drug-induced myasthenic syndromes were discussed.

Deficiency states may cause neuro-ophthalmologic symptoms and signs. The clinical and subclinical ophthalmic findings of vitamin A (retinol) deficiency are described among patients with recognized and unrecognized hepatic dysfunction (265). Although nyctalopia may suggest the underlying deficiency, the patient may present with unexplained bilateral visual loss and an otherwise unremarkable ocular examination. Patients with predisposing conditions such as hepatic dysfunction or malabsorption states should be monitored carefully and supplemented accordingly. Wernicke encephalopathy, presumably also a result of nutritional deficiency, manifests with ataxia, abnormalities of ocular motility, and acute confusion. Recently, the MRI features of the disorder were clarified (266-268). On T2-weighted images acutely, symmetrical bilateral hyperintense lesions are noted periaqueductally in the midbrain, in the hypothalamic/mammillary body region, and around the third ventricle and dorsal thalamus. Gadolinium enhancement of the mammillary bodies may be the only acute MRI finding. Late findings include substantial atrophy in these regions, especially of the mammillary bodies.

Lieb et al. (269) described a patient with the rare association of orbital myositis and giant cell myocarditis, a usually fatal syndrome. The authors recommended a high index of suspicion for giant cell myocarditis in patients with inflammatory orbital polymyositis in the absence of Graves disease.

A recent report in Science regarding the early diagnosis of Alzheimer’s disease with pupillary testing (270) has captured the imagination of the media and caused many questions to come the neuroophthalmologist’s way. In a study of 19 suspected Alzheimer patients and 32 age-matched noncognitively-impaired controls, Scinto et al. (270) found that 18 of their suspect group had a marked hypersensitivity in their pupil dilation response to tropicamide compared to only two controls. No information was provided regarding corneal findings, blink rate, dry eye, or iris color. In a different study (271), supersensitive constriction to dilute pilocarpine was noted among 21 probable Alzheimer’s patients compared to controls, but there was
substantial overlap. Caution is suggested and further corroborative studies are necessary before any pupillary test can be recommended as a diagnostic test for Alzheimer’s disease.

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Book Reviews


Dr. Henderson has dedicated the third edition of his text to his “three girl friends,” and the final product demonstrates the esteem in which he holds them. The text is divided into three sections, which deal with the diagnosis of orbital tumors, characteristics and treatment modalities for various individual tumors, and the surgical approach to these lesions.

The book begins with an excellent chapter on the historical and examination approach to all patients suspected of harboring an orbital lesion and should be required reading for all ophthalmologists in practice. The following chapters on orbital imaging and laboratory supplements contain up-to-date, if rather superficial, information on neuroimaging, echography, angiography, fine-needle aspiration biopsy, tumor markers, and molecular genetic analysis.

The second section composes the bulk of this text (19 chapters) and opens with a wonderful review of the 40-year Mayo Clinic orbital tumor series of 1,376 cases of orbital tumors. The following chapters concentrate on individual lesions, including vascular malformations and neoplasms, bony tumors of the orbit, neural sheath tumors, hematopoietic tumors, melanoma, primary and secondary epithelial neoplasms, metastatic carcinomas, and inflammatory tumors. Each type of tumor is reviewed nicely with summaries of its demographics, clinical features, imaging aspects, histopathology, treatment modalities (including new concepts on orbital radiation and chemotherapy for malignant lesions), and prognosis. The list of topics covered is quite complete; however, in keeping with the stated mission of the text, discussions of Graves’ orbitopathy, orbital trauma, and orbital infections are not included.

Completing the text is a chapter on surgical techniques for orbitectomy and orbitotomy. It also includes information on current carbon dioxide and yttrium aluminum garnet (YAG) lasers and combined neurosurgical/orbital approaches.

This extensive update of the previous edition is well written, easy to understand, and contains much practical, clinically relevant information. Supporting this are 430 high-quality photographs and diagrams, 35 of which are in color. I recommend this text as an addition to the library of neuro-ophthalmologists, orbital surgeons, and all who are interested in this spectrum of diseases.


This update of Yanoff and Fine’s previous atlas is a must for all ophthalmologists-in-training and is a clear, concise review of basic concepts and classic descriptions of a wide variety of disease entities. Although intended as a companion to their textbook, this atlas is itself worthy of study. This reviewer relied heavily on the first edition in preparation for both his written and oral board examinations.

The best thing about the second edition is that all of the photographs and figures (all of which are in color) are considerably enlarged over those in the previous atlas. Seventy-six new color pictures have been added as well.

The book contains 18 chapters, which begin with basic principles of pathology, congenital anomalies, granulomatous and nongranulomatous inflammation, and surgical and nonsurgical trauma. It ends with nice reviews of specific diseases: diabetes, glaucoma, ocular melanotic tumors, and retinoblastoma. Another nice addition from the first edition is that each of the remaining chapters, which focus on various anatomic sites within the eye and orbit, begins with a brief review of the normal anatomy and histopathology of that region.

I heartily recommend this atlas for all who need to begin, build on, or review their foundation in ocular pathology. Its clarity, organization, and excellent illustrations make it a truly worthy investment.

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Literature Abstracts


Dr. Newman and others examined blood samples from 135 Cubans with optic neuropathy as part of the recent epidemic neuropathy and found only a handful of cases with mitochondrial DNA mutations known to be associated with Leber's disease.


Four patients are described in the first article with a clinical picture of cat scratch disease but also intraocular inflammation and neuroretinitis. The patients were successfully treated with ciprofloxacin hydrochloride or, in one case, doxycycline hydrochloride. Dr. Grossniklaus reviews this and other reported ocular manifestations of Rochalimaea infection in the eye in his editorial.


Diplopia from skew deviation was experienced by five patients with acute vestibular neuritis. All eventually resolved their ocular symptoms with resolution of the vestibular disease.


Records of all 16 patients with superior oblique myokymia seen at Wilmer Ophthalmological Institute between 1976 and 1993 were reviewed. Follow-up was available for 14 patients and ranged from 3 to 29 years. Five of seven patients who had received no therapy were still symptomatic, and one of three patients treated medically continued to do well on carbamazepine. Four patients had superior oblique tenectomy with resolution of all symptoms after surgery. The authors suggest that this disease may be more protracted and disabling than previously thought and that surgical therapy may be more efficacious when symptoms are disabling.


A second series of 21 patients who underwent optic nerve sheath decompression for progressive ischemic optic neuropathy at Bascom Palmer Eye Institute is detailed. As they had found previously with 26 similar patients, in their hands surgery did not result in any significant improvement in visual outcome with most patients unchanged, two with modest improvement, and two with worsening of visual function. Based on their experience, the authors do not endorse the surgery for treatment of progressive ischemic optic neuropathy.

A very exacting critique of a recent article in ophthalmology linking smoking to nonarteritic ischemic optic neuropathy is given in this letter to the editor with some valid points advanced regarding control groups used. The authors of the original article (Ophthalmology 1194;101:779-82 abstracted for Journal of Neuro-ophthalmology) respond and challenge Dr. Johnson, Dr. Botelho, and Ms. Kuo to publish their own data, to which they refer in their letter as showing smoking not to be a risk factor for nonarteritic ischemic optic neuropathy.


Six patients who experienced profound oculocardiac reflex (3- to 10-second asystole) during extraocular muscle surgery were studied with four vagotonic maneuvers. Only carotid sinus massage correlated with increased oculocardiac reflex, producing significantly more bradycardia in the six patients than in controls. This test might be useful in predicting patients likely to experience profound oculocardiac reflex during extraocular muscle surgery.


The authors used a hand perimeter to quantitate degree of eye movement in Graves’ ophthalmopathy. They found this technique to produce much more precise measurements than the subject of assessments of endocrinologists or ophthalmologists.


Drs. Borodic and colleagues point out that a recently published report ("Serum Antibody Production in Botulinum A Toxin," Ophthalmology 1993;100:1861–6, previously abstracted for the Journal of Neuro-ophthalmology) which showed 57% incidence of detectable antibody to botulinum A toxin in patients receiving this medication is not as important a clinical observation as would be measuring "neutralizing" antibodies, which render patients unresponsive to further treatment with botulinum A injections. Drs. Siatkowski and associates reply.


Two patients with malignant melanoma developed bilateral visual loss with findings consistent with paraneoplastic retinopathy. They were studied with electroretinography and had testing of their sera in vitro with normal cadaveric retinal tissue. These patients had an IgG antibody reactive to retinal bipolar cells, in contradistinction to the usual antiretinal cancer antibodies that react with retinal ganglion and photoreceptor cells.

Painless Diplopia Caused by Extraocular Muscle Sarcoid. Patel AS, Kelman SE, Duncan GW, Rissmundo V. Arch Ophthalmol 1994;112:879-80 (July). [Reprint requests to Dr. A. S. Patel, Department of Ophthalmology, University of Maryland Hospital, 22 S. Greene St., Baltimore, MD 21201.]

A 43-year-old black woman presented with a 3-month history of diplopia. She had bilateral duction deficits and magnetic resonance imaging demonstrated enlargement of right superior, right inferior, and left medial recti, as well as lacrimal glands. Gadolinium gave diffuse enhancement of all rectus muscles. Thyroid function studies were normal as was a chest radiograph. Biopsy of the left medial rectus and lacrimal gland showed noncaseating granulomas and angiotensin-converting enzyme was elevated (2,700 nmol L⁻¹ s⁻¹). She was successfully treated with oral corticosteroids.

Four patients are described who developed ischemic optic neuropathy in one or both eyes after lumbar spine surgery, during which blood pressure was purposefully kept low to control bleeding. Blood loss was estimated at 2 liters in 3 patients, 2 of whom had transfusions with blood products. The authors review and catalogue the literature of similar cases (ischemic optic neuropathy after nonophthalmic surgery) and conclude that hypotension, planned or not, and/or blood loss are major risk factors for the development of postoperative ischemic optic neuropathy.


Twenty-two consecutive patients with biopsy-proven giant cell arteritis were studied with color Doppler, with results reported for ophthalmic artery, central retinal artery, and short posterior ciliary arteries. An abnormal ophthalmic artery flow with high peak velocity associated with turbulent flow suggestive of focal stenosis seems to be unique to patients with giant cell arteritis compared to normals and other patients with nonarteritic ischemic optic neuropathy.


A total of 6,536 visual fields from the 448 patients in the Optic Neuritis Treatment Trial during the first year of follow-up were analyzed for this report. Both affected and fellow eyes were tested on Humphrey Visual Field Analyzer machines. Many interesting observations emerge from the data, perhaps the most predictable being that the majority of affected eyes regained a normal visual field with time. More remarkable is the number of fellow eyes with field defects (nearly 70% at entry) and the number of chiasmal and postchiasmal field defects uncovered on at least one field during the testing period (13.2%).


In 1982, a 47-year-old woman with a three-year history of recurrent relative scotoma left eye was examined. Her subsequent history is given through 1993 when partial thromboplastin time was found to be prolonged and positive antiphospholipid antibodies were detected. No other laboratory tests were abnormal, including ANA, serum protein electrophoresis, protein S and C levels, and she seemed to improve on coumadin therapy.


A 35-year-old man with HIV and a complaint of blurred vision on examination was found to have bilateral proptosis with “radiologic examination” and ultrasonography demonstrating bilateral intraconal masses. Abdominal computerized tomography disclosed a mass, biopsy of which showed small cell, noncleaved, non-Hodgkin’s, B-cell lymphoma. A similar 35-year-old HIV-positive man had similar orbital findings and had similar pathologic findings on fine-needle orbital biopsy.


Retrospective chart review of 100 patients thought to have idiopathic orbital myositis revealed 75 patients with complete data and no con-
founding possible diagnoses (e.g., thyroid eye disease). In two thirds of patients, a single muscle was involved, and in about half the affected muscle functioned normally. In the other half there was about an equal distribution of paretic, restrictive, or combined paretic and restrictive myopathy. Their data suggest that early echography can show an enlarged muscle with normal function, but within days the muscle becomes paretic and later restricted. Two thirds of patients responded very well to oral corticosteroid therapy, and the authors advocate starting this therapy as soon as possible to avoid permanent restrictive changes in the muscles affected by thyroid eye disease.


The authors compare the size of extraocular muscles in 20 subjects (39 orbits) using magnetic resonance imaging with surface coil technique and echography.

Relapsing and Remitting Central Retinal Artery Occlusion. Werner MS, Latchaw R, Baker L, Wirtschafter JD. Am J Ophthalmol 1994;118:393-5 (Sept). [Inquiries to Dr. J. D. Wirtschafter, University of Minnesota, Box 493, 420 Delaware St. S.E., Minneapolis, MN 55455-0501.]

A 66-year-old patient with several episodes of amaurosis fugax was found to have multiple confluent cotton-wool spots below and above his cilioretinal artery with normal visual field. After verapamil and aspirin therapy, he returned with stable visual function but worsening retinal picture. Carotid ultrasonography found a 30-50% occlusion of the internal carotid artery. He underwent transfemoral catheterization and infusion of urokinase into the left ophthalmic artery, which was complicated by a transient expressive aphasia. Magnetic resonance imaging 24 h later showed temporal lobe edema. He did well visually, however. The authors discuss this rather unconventional treatment.


This case report involves a woman who presented at age 23 with sudden retrobulbar pain and visual loss in the left eye, which was treated as optic neuritis in 1986 with oral corticosteroids. One month later, computerized tomography and magnetic resonance scanning showed a mass in the left orbital apex, and laboratory workup was negative for sarcoidosis or vasculitis. Needle biopsy was "not diagnostic," and her vision did return to near normal. Her acuity worsened within several months, and exploration of the orbit was negative for a mass. Visual function again improved on oral corticosteroids. Over the following two years, the patient had intermittent treatment with corticosteroids but became cushingoid. Repeat imaging again demonstrated a posterior orbital mass; three years after original presentation, this was definitively biopsied and subtotally resected via a frontal craniotomy. In the year following, two more surgeries were performed via the orbit for recurrence of the tumor, and she ultimately developed ocular motility problems and optic atrophy with subnormal visual function. Pathologic diagnosis was an enterogenous cyst believed to have started intracranially with extension into the superior orbital fissure and orbital apex, the first reported case in this location. The entity is discussed in detail.

Fixation Duress in the Pathogenesis of Upper Eyelid Retraction in Thyroid Orbitopathy. A Prospective Study. Hamed LM, Lessner AM. Ophthalmology 1994;101:1608-13 (Sept). [Reprint requests to Dr. L. M. Hamed, Pediatric Ophthalmology Clinic, Department of Ophthalmology, University of Florida College of Medicine, Box 100284, JHMSC, Gainesville, Fl. 32610-0284.]

Six patients with thyroid eye disease and presumed "fixation duress" that caused upper lid retraction are described. Each had improved lid retraction in downgaze and significant supraduction deficit bilaterally. All had strabismus, and bilateral inferior rectus recessions were performed that improved the eyelid position. This condition is defined and discussed.

Spontaneous Hemorrhage within the Rectus Muscle. Hakin KN, McNab AA, Sullivan TJ. Ophthalmology 1994;101:1631-4 (Sept). [Correspondences to Dr. A. A. McNab, 200 Drummond St., Carlton, Melbourne, Victoria, 3053, Australia.]
Three patients (ages 31, 68, and 76) who had an acute intramuscular hemorrhage involving one rectus muscle, are presented in detail, including results of computerized tomographic and magnetic resonance scans. One patient had hypertension and another a history of intense exercise the day before the hemorrhage, but the third had no risk factors. All had no change in visual function and resolved spontaneously. This entity is discussed.


Four patients are presented, with pathology at or below the level of the pons, who demonstrated a hypertropia pattern not consistent with superior oblique muscle dysfunction. They all had significant cyclotorsion. The authors discuss possible mechanisms for these findings in cases of skew.

Orbital Hemorrhage Induced by Barotrauma. Andenmatten R, Piguet B, Klainguti G. *Am J Ophthalmol* 1994;118:536-7 (Oct). [Inquiries to Dr. B. Piguet, University Eye Clinic, Jules Gonin Hospital, Av. de France 15, 1004 Lausanne, Switzerland.]

A 22-year-old inexperienced diver felt pain in the right orbit during a dive to 20 m. She had ptosis and limited supraduction of the right eye as well as conjunctival hemorrhages. Computerized tomographic scanning showed a probable hemorrhage in the superior right orbit, which the authors believe to be subperiosteal. It seems it might alternatively be within the superior rectus muscle, given the motility disorder. Fortunately, it resolved spontaneously.


Another point/counterpoint letter to the editor criticizing the economic design of the Ischemic Optic Neuropathy Decompression Trial, which in essence expects patients' private insurance to foot the bill for all visits and surgery, a decidedly non-minimalist attitude in an insurance climate of capitation and emphasis on primary care. Dr. Kelman responds that the care dictated by the trial falls within the realm of care "normally provided by neuro-ophthalmologists to patients with nonarteritic ischemic optic neuropathy" and that data analysis is covered by the National Eye Institute funding. Nevertheless, it seems to this practicing neuro-ophthalmologist that Dr. Diegel has a point, as the number of visits and testing done on patients in the trial is significantly more than seems to be medically necessary when such patients are followed in the community.


For those of us wondering about the cost effectiveness of scanning patients with optic neuritis vis-à-vis treatment decisions, this letter to the editor and reply by Dr. Beck are required reading. Dr. Coyle notes previous studies showing much greater conversion to multiple sclerosis for women than men with an initial optic neuritis and contends that not separating gender and perhaps race as well in the Optic Neuritis Treatment Trial may lump instead of splitting in terms of outcomes. He also suggests forgoing the magnetic resonance scan and using the three days of high-dose intravenous corticosteroids in all medically approved patients with optic neuritis. In a vigorous reply, Dr. Beck notes that the results to date of the Optic Neuritis Treatment Trial are valid no matter how one lumps or splits the groups and that their patients' conversion to multiple sclerosis has been similar for men and women. Furthermore, the MR may be most useful in demonstrating which patients truly do not and will not have multiple sclerosis, as its predictive value has been excellent to date in the trial.


An 11-year-old girl with a several-week history of right lower eyelid edema was found to have a subcutaneous pulsatile mass in this location. Color Doppler, magnetic resonance scanning, and right arteriogram demonstrated an arteriovenous malformation of the inferior orbit and the right lower eyelid. The lesion enlarged, and the patient under-
went successful polyvinyl alcohol embolization followed 48 h later by resection.


Six patients with acquired, visual-disabling nystagmus underwent retrobulbar botulinum A injections. Five of six patients rated their improvement good or excellent, and two patients with oculopalatal myoclonus had a prolonged therapeutic response (four to six months) compared to that of the other patients (six weeks to four months) with diagnoses of pontine hemorrhage and multiple sclerosis. The authors feel this is a reasonable treatment alternative for those patients and recommend it be tried as an adjunct to retroequatorial rectus muscle recession for acquired nystagmus.

Epithelioid Sarcoma of the Orbit. White VA, Heathcote JG, Hurwitz JJ, Freeman JL, Rootman J. Ophthalmology 1994;101:1680-7 (Oct). [Correspondence to Dr. V. White, Department of Pathology, Vancouver General Hospital, 910 West 10th Ave., Vancouver, BC V5Z 4E3, Canada.]

Two patients, ages 17 and 34 years, are presented with a subacute temporal orbital mass, in each of whom it was pathologically identified as epithelioid sarcoma. One patient died of her disease within 2½ years. The authors discuss this tumor and note that these are the first cases reported with primary orbital involvement.


This major review is replete with excellent color optic disc photographs. Good magnetic resonance studies of associated anomalies are also included. This is a very nice reference.


Two young men are presented with findings of retinal vasculitis (arterial and venous sheathing, hemorrhage, branch arterial occlusion) who ultimately developed central nervous system symptoms and were found on brain biopsy to have T-cell lymphoma. The authors review the literature in regard to marker-specific intraocular lymphoma and its retinal findings. They conclude that lymphoma needs to be considered in the differential diagnosis of any patient with unexplained retinal vasculitis.


A 19-year-old woman, with progressive visual loss dating to age 3, is discussed. She was found to have the Wallace mutation at base pair 11778 (mitochondrial DNA). The authors discuss our expanding knowledge about and definition of Leber's hereditary optic neuropathy and suggest it may be appropriate to test for this disease in both men and women with unexplained optic neuropathy.

Echinococcus Cysts of the Orbit and Substernum. Mohammad AEA, Ray CJ, Karcioglu ZA. Am J Ophthalmol 1994;118:676-8 (Nov). [Inquiries to Dr. Z. A. Karcioglu, Department of Ophthalmology, Tulane University Medical Center, 1430 Tulane Ave., Rm. 5016, New Orleans, LA 70112-2699.]

A 15-year-old girl with "progressive right proptosis" was found to have a cystic mass of the anterior, medial right orbit. This was removed, and pathologic diagnosis was an Echinococcus cyst.


Two patients are described with inferior rectus muscle overaction following cataract surgery. The author postulates that the local anesthetic agent may have induced a degeneration of some muscle fibers in the inferior rectus muscle, which ultimately resulted in overaction when these fibers regenerated.
Letter to the Editor

Optic Neuritis Treatment Trial

To the Editor:

I enjoyed the recent editorial about the Optic Neuritis Treatment Trial by Dr. Savino (1), and would like to add a few comments.

Prior to the publication of the results showing a protective effect of high dose steroids against MS in patient with MRI abnormalities (2), life was fairly simple. Those of my optic neuritis patients who wished to have more rapid recovery of vision opted for steroids. I would discuss the data concerning the probability of developing MS (3), but would actively discourage the patient from further investigations such as MRI for two reasons. First, the results in an otherwise neurologically asymptomatic patient were of uncertain clinical significance. Second, I wished to avoid labeling the patient with a chronic and essentially untreatable disease in the present health care climate, particularly considering the issues surrounding preexisting conditions. I would not document the content of the discussions in the patient's chart, for similar reasons.

The new information about the usefulness of MRI in predicting who might benefit from high dose steroids is very exciting. I would agree with Dr. Savino that in an ideal world one would like to obtain an MRI on every patient presenting with optic neuritis, and make a decision about high-dose steroid treatment based upon the MRI results. However, consider the following, increasingly typical scenario.

Case Presentation

A 30-year-old healthy woman presented on March 15, 1994, with a 3-day history of pain on eye movements, followed by visual loss OS. Examination OD was normal. Examination OS showed a typical optic neuropathy, with decreased central vision, dyschromatopsia, a large central scotoma, and a relative afferent pupillary defect. There was no proptosis nor any ocular motor abnormalities. Slit lamp and fundus examination were normal.

A diagnosis of retrobulbar optic neuritis was made, and issues surrounding the visual and neurologic implications of treatment with high dose steroids were discussed at length. The patient elected to undergo steroid therapy for more rapid return of vision, regardless of the results of an MRI scan. Nevertheless I recommended to the patient's primary care physician that an MRI scan be arranged in order to assess whether the steroids might also protect the patient against MS.

The patient received methylprednisolone 500 mg b.i.d. i.v. infusion for 3 days as an outpatient. About 1 week after I had first seen the patient, I received a call from the Quality Assurance Nurse at the patient's health plan asking for more information to evaluate the necessity of an MRI. I explained the recent literature to her and faxed a copy of the relevant article.

When I saw the patient on April 12, 1994, visual acuity, visual fields, and color vision had all returned to normal. Approval had still not been obtained for an MRI (and I doubt at this stage that it will be).

Although the approach put forward by Dr. Savino is "medically correct," I fear that we will, de facto, be forced to take a different tack. As much as I dislike nonmedical constraints on our patient management, the realities are difficult to escape:

1. We will find, as I have done already, that the health carriers may not approve an MRI in this situation, and, if they do, the approval will often be delayed. In either case a decision about steroids will need to be made independent of the MRI outcome.

2. It will not take long for "cost-effectiveness" to raise its ubiquitous head. Where I practice, the cost of fee-for-service bid outpatient steroids is about $1,230.00 (qd steroids are even cheaper, at about $825.00), whereas the cost of a brain MRI with contrast is $1,410.00. Obviously, it is cheaper to give steroids to every patient who presents with optic neuritis, than to give every patient an MRI and a further subgroup steroids. The fact that many neuro-ophthalmologists have now abandoned inpatient q.i.d. steroids, even though this was the only regimen tested by the ONTT, is evidence that our day-to-day management of these patients is already being influenced by factors other than hard medical data.

3. Patients with optic neuritis come from a young mobile section of the population, with a high probability of changing employment and health insurance over any given period. At this point the Clinton health plan, with its promise to rid our vocabulary of the term "preexisting condition," is still a glint in the administration's eye. One should therefore still consider the implications of placing evidence of a possible chronic, es-
sentially untreatable and unpredictable disease in the patient's medical record, particularly if the patient currently has no significant clinical problems. It is fruitless to try to explain to insurance companies that having white matter lesions does not necessarily mean clinical MS. Having every patient with optic neuritis undergo an MRI might result in a group who finds itself virtually uninsurable.

Because of these issues I am finding myself more and more frequently recommending high-dose steroids to all patients with significant visual loss from optic neuritis, to "hasten the recovery of vision." I discuss the MS issue, informing the patient that a subgroup has been found in whom the treatment seems to protect against clinical MS. I then give the patient the option of having a MRI, discussing some of the nonmedical issues, and knowing full well that, even if the patient elects to have neuroimaging, it will probably be approved belatedly or not at all.

I take some comfort in the fact that at least this "shotgun" approach is safe, since high-dose steroids pose very little risk in these young healthy patients, and that at least some of my patients (which ones??!) might be protected from clinical MS. It is certainly less than ideal however, that Dr. Levi's simple management algorithm, based on good data, is subject at present to so much distortion by nonmedical realities.

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REFERENCES

Editorial Comment to "Optic Neuritis Treatment Trial"

The letter of Dr. Leah Levi concerning the dilemma now facing the clinician attempting to manage a patient presenting with the first attack of optic neuritis prompted the following comments. Having recently attained the Emeritus rank at Bascom Palmer, I thought I might simply not respond to the problem, but because this problem is of such magnitude in the practice of neuro-ophthalmology, perhaps the reader will be patient with me as I express my own personal approach and thoughts about this problem.

First, let us briefly look at the initiation of the Optic Neuritis Treatment Trial. At the outset, I was invited to participate in the study, but my personal experience with the use of steroids in patients with optic neuritis had convinced me that of three things: (1) there are many types of optic neuritis and it is not a single disease entity by any means, (2) I believe that experience has shown me that in certain types of optic neuritis, which could be identified by a careful history and office examination, the use of steroids was definitely helpful to the patient, and (3) I therefore felt I could not participate in a study in which patients were going to be differentiated into treatment versus control groups, because I could not elect to manage a patient as a control (i.e., withhold steroid therapy) in a circumstance where I felt this therapy would definitely be helpful. I therefore declined to participate in the study. At least one other neuro-ophthalmologist I know told me the same thing, and therefore it should be understood that at least some clinicians felt that steroids given in the proper manner were so helpful that their input was, at their own request, not included in the study. One might say that this was a small number and should not be considered in interpreting the results, but I am simply pointing this out as a matter of record.

Finally, after completion of the Optic Neuritis treatment trial, the major conclusions as I understand them were as follows: (1) Oral steroids in a dose of about 70 mg/day for 2 weeks not only did not show any definite helpful effect in acute optic neuritis but were subsequently thought to be associated with an increased incidence of later developing multiple sclerosis. This conclusion threw a huge wet blanket across ophthalmology, so much so that many clinicians who wanted to treat patients with optic neuritis with steroids, even under severe circumstances, were afraid to do so. (2) However, the trial also showed that intravenous megadose steroids, in a dose of at least 1,000 mg/day for 3 days, followed by an oral dose taper to 2 weeks showed not only more rapid resolution of the visual deficit early on, but later was reported to have decreased the incidence of subsequently developing multiple sclerosis. The latter point was discussed in detail in Dr. Levi's letter.

Now, it would seem to me that logic would cause one to come to certain conclusions from the above data. First of all, steroids are well known to have excellent bioavailability when given by mouth so that there is no significant difference in
sentially untreatable and unpredictable disease in the patient's medical record, particularly if the patient currently has no significant clinical problems. It is fruitless to try to explain to insurance companies that having white matter lesions does not necessarily mean clinical MS. Having every patient with optic neuritis undergo an MRI might result in a subgroup having white matter lesions identified by a careful history and office examination. However, the use of steroids was definitely helpful to the patient, and I therefore felt I could not participate in a study in which patients were going to be differentiated into treatment versus control groups, because I could not elect to manage a patient as a control (i.e., withhold steroid therapy) in a circumstance where I felt this therapy would definitely be helpful. I therefore declined to participate in the study. At least one other neuro-ophthalmologist I know told me the same thing, and therefore it should be understood that at least some clinicians felt that steroids given in the proper manner were so helpful that their input was, at their own request, not included in the study. One might say that this was a small number and should not be considered in interpreting the results, but I am simply pointing this out as a matter of record.

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blood or tissue level concentrations when given by mouth as compared to intramuscular or intravenous administration. Therefore, if 70 mg/day by mouth does no good—whereas 1,000 mg/day intravenously does—the first conclusion should be not that the difference in outcome is due to different routes of administration but that the difference is more reasonably due to the dosage employed. In other words, 70 mg/day may be too little, and 1,000 mg/day may be too much, and the proper dosage could lie somewhere in between. The next conclusion to my mind would be that if a small dose of steroids puts a patient at greater risk for developing multiple sclerosis where a larger dose of steroids reduces the risk for later developing multiple sclerosis, that we are now in the realm whereby one can draw from statistics any conclusion he might desire. It does not appear to logic to say that a little dab of steroids will do you in, whereas a huge dose will turn the coin upside down with regards to later prognosis.

I have found that use of subtenon’s steroids (e.g., giving 1 ml or 40 mg of subtenons aqueous triamcinolone) has been very helpful in many cases of optic neuritis and this has been used in my practice for well over 20 years with no problems of consequence whatever. See: Smith JL, McCrary JA, Bird AC, et al. Subtenon steroid injection for optic neuritis. Trans Am Acad Ophthalmol Otol 1970; 74:1249–53. Fortunately, this route of steroid administration was not evaluated in the optic neuritis treatment trial, so that the clinician who desires to employ that route can continue to do so without having to be concerned about “bad press” from a major cooperative study, as it simply has not been evaluated in such a study to date. I use a 3-ml syringe with a #25 gauge needle ½ in. long and inject 1 ml aqueous Kenalog at the junction of outer and middle thirds of lower lid in exactly the same way as in giving retrobulbar anesthesia, and have found that one injection often will last 2–6 weeks, and seldom needs to be repeated in these cases.

It is very important, of course, to not only take a complete history—was there an antecedent upper respiratory infection a few weeks before onset of the optic neuritis?—and a careful examination—are there any cells in the vitreous on a careful slit lamp examination?—for both of these points favor an inflammatory (i.e., infectious) pathogenesis to the optic neuritis and are votes against a demyelinating disease. Certainly, pure papillitis or neuroretinitis are votes against demyelination, whereas a pure retrobulbar optic neuritis with a normal appearing disc early on is more likely to be followed later by multiple sclerosis in the particular age group under consideration.

Finally, I would like to say at least a few words about magnetic resonance imaging and optic neuritis. I personally do not think every patient presenting with an initial attack of clinically typical optic neuritis needs to have an MR scan. This not only relates to the significant expense of MR imaging, but also to the fact that the presence of a few “UBOs” or white matter lesions in these patients is a difficult correlate with the subsequent clinical diagnosis of multiple sclerosis. In other words, some UBOs may be present in individuals who do not have multiple sclerosis, and also some patients who subsequently turn out to have undoubted multiple sclerosis may not show any significant abnormalities on MR scanning early on. Therefore, I am quite in agreement with Dr. Levi that the decision as to whether to obtain an MR scan in the patient with optic neuritis must be individualized by the physician seeing that particular patient. It simply is not fair with the myriad variables seen in patients within the clinical spectrum of optic neuritis to make a hard and fast rule that every patient must or should absolutely not have an MR scan. This is a clinical decision that should be made by the neuroophthalmologist seeing that particular case.

I believe there will be a place for treating certain patients with optic neuritis with subtenons steroids and also other patients with larger doses of oral steroids than have been customarily employed in the past but doing this as an outpatient while carefully following the patient and only for a few days. For example, giving a patient with a severe loss of vision 200–300 mg/day of oral prednisone for 3 days and then seeing the patient again would not be unreasonable in my opinion. If the medicine is going to work, this will usually be evident within 2–3 days, and if no improvement has been noted in that time, the medicine can usually be simply stopped at that point, without the necessity for the taper needed with more protracted use.

I am sure that not everyone will agree with these personal experiences. However, there are some things we have learned by experience that may be worth considering by others and not simply discarding them up front because of one or two studies. I pray that wisdom will prevail in the practice of medicine, and no matter what external forces come against the clinician, a good doctor will still be able to cure sometimes, to relieve often, and to comfort always.

J. Lawton Smith, M.D.
Editor-in-Chief Emeritus

LETTERS TO THE EDITOR 263

Erratum

Uhthoff and His Symptom
John B. Selhorst, M.D., and Robert F. Saul, M.D.

On p. 63, the last sentence of the abstract was printed incorrectly. It should read: "This study and its companion in the publication show that, independently, a metabolic byproduct of exercise or increases in body temperature cause a reversible conduction block in demyelinated optic nerves and result in temporary loss of vision."

We regret any confusion caused by this error.
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