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Surgery for Idiopathic Intracranial Hypertension

Paul W. Brazis, MD

Idiopathic intracranial hypertension (IIH), a condition in which the intracranial pressure rises without explanation, is usually successfully treated with weight reduction or medications designed to reduce intracranial pressure. However, there are instances when surgical intervention, consisting usually of lumboperitoneal shunt (LPS), ventriculoperitoneal shunt (VPS), or optic nerve sheath fenestration (ONSF), is indicated. Dural venous sinus stenting has also been successfully used in some patients (1–7).

In this issue of the *Journal of Neuro-Ophthalmology*, Wilkes and Siatkowski (8) report a patient with IIH whose vision deteriorated after medical therapy and ONSF and perhaps even after VPS. The authors caution that patients who appear to have further visual loss after ONSF should be considered promptly for VPS. Also in this issue, Gellrich et al (9) report experimental evidence that ONSF may cause a significant reduction in the number and size of retinal ganglion cells and amacrine cells in rats. On that basis, they caution clinicians against using ONSF.

Yet there is extensive anecdotal evidence that ONSF and shunt procedures seem to arrest and sometimes even reverse optic neuropathy in IIH. Whether one type of procedure is more effective than the other is unknown, as no trial has ever compared them. I will summarize the evidence, such as it is.

**LUMBOPERITONEAL SHUNT**

LPS has reversed or prevented visual loss in IIH but carries a high rate of shunt-related complications (10–17).

In a retrospective study of 27 patients (12), LPS was successful in alleviating symptoms in all patients. No patient with a functioning shunt complained of shunt-related symptoms. Among 30 patients who underwent LPS (11), 14 had impaired visual acuity preoperatively and 71% improved by at least 2 Snellen lines. Worsening of vision occurred in only 1 eye. Of 28 eyes with abnormal Goldmann perimetry, 64% improved and none worsened. The incidence of serious complications was low, but the major drawback was that 30 patients underwent a total of 126 revisions with a mean revision rate of 4.2 per patient.
The need for frequent shunt revisions occurred in a study of 37 patients who underwent 73 LPS and 10 VPS procedures in 6 institutions (16), in which only 14 patients remained “cured” after a single surgical procedure. The average time between shunt insertion and shunt replacement was 9 months, but 64% of the shunts lasted less than 6 months. Recurrent papilledema or increased cerebrospinal fluid pressure on lumbar puncture (55%) and low-pressure headache (21%) were the most common indications for reoperation. Other reasons were infection, abdominal pain, radicular pain, operative complications, and cerebrospinal fluid leak. The vision of most patients improved or stabilized postoperatively. However, 3 patients who had initially improved subsequently lost vision, 6 had a postoperative decrease in vision, 2 patients improved in 1 eye but worsened postoperatively in the other eye, and 4 lost vision despite apparently adequate shunt function. Shunt failure with relapse of IIH occurred as late as 7 years after insertion. Another study (13) found that 36 patients who underwent LPS required 85 shunting procedures with an overall complication rate of 52% and a failure rate of 48%.

Taking into full account the reported literature on LPS in IIH, shunt failure appears to be common (cumulative risk 37%), but most failures occur within 2–3 months of the initial procedure and only rarely is the first revision required more than 1 year after the initial procedure (12). LPS failure can apparently be successfully treated by repeat LPS or by ONSF (see below).

VENTRICULOPERITONEAL SHUNT (VPS)

VPS also appears to be effective in controlling IIH and may have fewer complications than LPS.

Among 21 consecutive patients who received LPS and 21 who received VPS with frameless stereotactic image guidance (18), there was a 2.5-fold increased risk of shunt revision and a 2.8-fold increased risk of shunt obstruction in LPS. However, LPS and VPS had a similar risk of overdrainage, distal catheter migration, and shunt infection. This first comparison of stereotactic VPS and LPS suggests that VPS placed with image-guided stereotaxy is associated with a lower risk of shunt obstruction and revision.

Among 17 patients treated with VPS for IIH and followed for up to 12.8 years (mean 6.5 years) (19), VPS was effective for all clinical manifestations of IIH. Seven patients required 1 or 2 (a total of 9) surgical revisions, all within the first 1.9 years (mean of 6 months) of shunt placement. One revision was needed because of malposition of the ventricular catheter, 6 because of failure of the peritoneal catheter, and 2 because of suspected shunt infection. The survival time of the most recent shunt placed in each patient was 1.8–12.8 years (mean 6.3 years). Four patients developed low-pressure headache due to over-drainage, a problem resolved by increasing the opening pressure of the valve.

However, VPS shunt failure was common in a report of 21 patients who underwent 32 ventricular shunting procedures (20 VPS, 10 ventriculoatrial, and 2 ventriculo-pleural) for IIH (20). Although all patients experienced relief of headache, 10% of VPSs failed at 3 months after insertion, 20% by 6 months, 50% by 12 months, and 60% by 24 months. Shunt revision was due to distal obstruction in 67%, overdrainage in 20%, and distal catheter migration or CSF leak in 6.5%. In a review of 9 VPS cases (21), 6 patients required 9 shunt revisions because of infection in 5, valve dysfunction in 2, distal obstruction in 1, and ventricular catheter malpositioning in 1.

Despite the apparently frequent problems with CSF shunts, they are being placed more frequently for IIH in the United States (22), perhaps because their efficacy is being recognized. VPS is supplanting LPS because revisions are required less often, shunt obstructions occur less often, and low pressure headache may be controlled by the programable shunt. At the Jacksonville Mayo Clinic, we have shifted to doing stereotactic VPS instead of LPS for IIH.

OPTIC NERVE SHEATH FENESTRATION

ONSF has also been reported to prevent deterioration of vision and, in some cases, improve visual function in patients with IIH (23–35).

In a study of 28 patients who underwent 40 ONSFs (21), papilledema disappeared or was strikingly reduced in 86% of patients. Visual acuity improved in 30% of eyes, remained stable in 55%, and declined in 15%. However, 10 eyes continued to lose visual acuity or visual field in the postoperative period. In another study of 23 patients (29), 91% showed visual improvement postoperatively. Strikingly, more than half of these eyes demonstrated improved visual function in both eyes after unilateral ONSF. ONSF improved vision in 6 patients who failed to recover vision after LPS.

In 17 patients with severe visual acuity or field loss from IIH (26), ONSF produced improvement or stabilization of visual acuity in 97%. Among 12 patients whose LPS had failed to control visual loss in another series (27), ONSF improved vision in all patients. In a series of 9 patients (30), ONSF brought about improvement or stabilization of vision in all but 1 patient. Among 158 ONSFs in 86 patients with IIH (36), visual acuity stabilized or improved in 94% of eyes and visual fields stabilized or improved in 88%.

ONSF appears to be more effective in preserving visual function when papilledema is not chronic. Among 69 eyes with acute papilledema in one series (34), ONSF produced improved visual function in all, but among
32 eyes with chronic papilledema, only 10 improved (34). Moreover, repeat ONSFs were necessary in 13 eyes because of initial failures.

The results for ONSF are not uniformly good. In 29 patients in one series (25), visual acuity improved in only 14% and worsened in 10%. There were 4 repeat ONSFs in which vision was lost in 1 eye.

Long-term follow-up data suggest that ONSF may not be as effective as originally claimed and that up to 33% of patients who show initial improvement in visual function will later show deterioration (32,33). Some late failures may be prevented by better and different operative techniques (31,33). In a study of 20 eyes of 14 patients (11 with idiopathic IIH and 3 with dural venous sinus occlusion) (23), visual function improved or stabilized in 17 and deteriorated in 3. Four patients required ONSF despite previous shunting or subtemporal decompression. Two patients required shunting or subtemporal decompression after ONSF because of visual failure. No patient lost vision as a direct complication of surgery.

Shunting may be successful in preventing further visual loss in eyes whose vision has failed despite ONSF. Among 108 patients who underwent ONSF (29), 5 had progressive visual loss afterward. In 1 of these patients, emergency LPS resulted in full visual recovery and in 3 visual loss stabilized. In reviewing the reported literature of patients with IIH in whom ONSF had failed, these authors (29) found that 4 of 7 patients sustained no improvement in vision despite various treatments, including shunts. Among 28 patients in another series (24), 6 lost vision after ONSF and only 1 had recovery of vision after shunting. Intravenous corticosteroid treatment appeared to enhance visual recovery in 1 patient whose vision declined after ONSF (37). The balance of opinion favors shunt over repeat ONSF if the first ONSF has failed.

Persistent complications of ONSF appear to vary widely from one series to another and may be visually damaging. In a series involving ONSF in 86 patients (36), diplopia occurred in 30 patients, with 87% resolving spontaneously. Only 1 eye had permanent severe visual loss from presumed traumatic optic neuropathy. One patient had total ophthalmoplegia and blindness after surgery that completely resolved over 1 month with corticosteroid therapy.

Others have reported more dire complications. In a series of 24 patients with IIH who required ONSF (35), 44% of eyes had complications including choroidal folds, macular edema, and subretinal hemorrhage, leading to persistent new visual loss in 8 eyes. In a series of 38 eyes (38), 15 had postoperative problems including central retinal artery occlusions (6%), tonic pupils (11%), and temporary ocular duction deficits (29%). Eyes that had undergone prior ONSF were more likely to have retinal vascular occlusions (67%) than those without a previous operation.

Taking account of the reported literature, it appears that approximately one third of patients undergoing ONSF will not experience headache relief and only about 75% of ONSFs appear to be functioning 6 months after surgery, as judged by loss of vision or worsening headache. The probability of an ONSF functioning steadily decreases thereafter, such that 66% are functioning at 12 months, 55% at 3 years, 38% at 5 years, and 16% at 6 years after surgery (32). Although patients may be treated with a second ONSF after initial failure, eyes that have more than 1 ONSF are less likely to improve after surgery and are at high risk of retinal vascular occlusion.

It is evident that LPS, VPS, and ONSF may improve vision and prevent deterioration of vision in patients with IIH. (Venous sinus stenting may be effective in selected patients, but the reported literature is too sparse to allow reasonable assessment.) Each of these procedures has its advantages and disadvantages and all may fail in time. No matter what treatment is used, patients with IIH must be followed carefully as treatment failure may occur even much later. Until a prospective, randomized study comparing ONSF with shunting is performed, the question of which surgical procedure is best for the treatment of IIH will remain unanswered.

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Degeneration of Retinal Ganglion Cells After Optic Nerve Sheath Fenestration in an Experimental Rat Model

Nils-Claudius Gellrich, MD, DDS, Constantin Stuehmer, DDS, Kai-Hendrik Bormann, DDS, Isabella Mücke, MD, Alexander Schramm, MD, DDS, Ulf Theodor Eysel, MD, and Martin Rücker, MD, DDS

Background: Optic nerve sheath fenestration (ONSF) is a surgical procedure that is sometimes performed in patients with optic disc edema from increased intracranial pressure. The objective of this study was to assess the consequence of ONSF on optic nerve axons, retinal ganglion cells (RGCs), and retinal amacrine cells.

Methods: The optic nerves of 22 male Wistar rats were assigned to one of three groups. In Group 1 (n = 12), the rats underwent unilateral ONSF. In Group 2 (n = 10), the rat optic nerves were unilaterally exposed but were not operated on. Group 3 (n = 22) consisted of the optic nerves of Group 1 and Group 2 rats that were neither operated on nor exposed. Thirty days later, a cresyl violet staining method was used to assess the number and sizes of RGCs and amacrine cells. Optic nerve axons were assessed by means of glial fibrillary acidic protein (GFAP) immunoreactivity.

Results: ONSF was associated with a significant reduction ($P < 0.05$) in the number and size of RGCs and amacrine cells. Optic nerve axons were undisturbed.

Conclusions: Although ONSF does not apparently injure the optic nerve axons, loss and shrinkage of RGCs is a caution when considering ONSF as a treatment.


The arachnoid and subarachnoid spaces around the optic nerve communicate freely with the intracranial subarachnoid space via the optic canal. For this reason, elevated cerebrospinal fluid (CSF) pressure can be transmitted to the optic nerve. The induced papilledema can result in visual loss. Intraorbital optic nerve sheath fenestration (ONSF) is a procedure that is often performed as an alternative to CSF shunting to relieve CSF pressure around the optic nerve in patients with idiopathic intracranial hypertension (IIH) (1–4). The benefit of ONSF, however, remains controversial due in part to variations in clinical outcome and in part to the poor understanding of its underlying mechanisms (6–8). The purpose of this study was to quantitatively assess the effect of ONSF on retinal ganglion cells (RGCs) and optic nerve axons in a rat model.

METHODS

Animals

All animal procedures were approved by the responsible ethics committee and were conducted in accordance with the German Protection of Animals Act and the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publication No. 85-23, revised 1985). The study involved 22 male Wistar rats (Charles River, Sulzfeld, Germany) weighing 300–350 g. The animals were housed singly in cages. They were given access to tap water and a commercial pellet diet ad libitum (Altromin, Lage/Westphalia, Germany).

Randomization

In a randomized fashion, one orbit was surgically accessed in each animal. In 12 male Wistar rats, an optic nerve sheath fenestration procedure was performed using a 2-mm longitudinal incision (Group 1). In an additional 10 male animals, the optic nerves were exposed on one side but were not operated on (sham surgery) (Group 2). The 22 optic nerves that were neither operated on nor exposed served as controls (Group 3). After a survival period of
30 days, the animals were anesthetized again, and the eyes and intraorbital optic nerves were assessed histologically.

**Surgical Preparation**

The rats were anesthetized with chloral hydrate (400 mg/kg body weight intraperitoneally), and their heads were fixed in a stereotaxic frame. A median frontal incision was made to expose the superior orbital rim. The superior orbital vein was identified and preserved. The retrobulbar space was accessed, and a large portion of the Harderian gland was removed, allowing the surgeon access to the eye muscle cone. Once the eye was gently pulled forward, the ocular muscles over the optic nerve were detached and held apart with a blunt hook so that only the retractor bulb muscle remained close to the optic nerve. Care was taken to maintain retinal perfusion during this maneuver. The retractor bulb muscle was then cut 2 mm behind the posterior portion of the eye and separated from the optic nerve.

In Group 1 animals, ONSF was performed using magnifying lenses and microsurgical instruments, in particular, a 23-gauge MVR blade. Two millimeters proximally to the optic nerve head, a rectangular window of dura and arachnoid measuring 2 mm in length and 1 mm in width was excised from the bulbous portion of the optic nerve with preservation of the pia mater. Throughout the procedure retinal perfusion was maintained as monitored by ophthalmoscopy. There was no bleeding in the immediate vicinity of the optic nerve. The swinging flashlight test was used to detect relative afferent pupillary defects before surgery, immediately after surgery, and before paraformaldehyde perfusion (30 days after surgery).

**Histologic Preparation**

Unless otherwise stated, all chemicals were obtained from Sigma (Deisenhofen, Germany) and were of the highest commercially available purity. After in vivo perfusion with heparinized Ringer’s lactate solution (0.2% Liquemin), the rats were perfused with a fixative containing 4% paraformaldehyde. The perfusion-fixed eyes were detached and held apart with a blunt hook so that only the retinal tissue remained close to the optic nerve. Care was taken to maintain retinal perfusion during this maneuver. The specimens were then processed as described below for histological analysis.

The rats were anesthetized with chloral hydrate (400 mg/kg body weight intraperitoneally), and their heads were fixed in a stereotaxic frame. A median frontal incision was made to expose the superior orbital rim. The superior orbital vein was identified and preserved. The retrobulbar space was accessed, and a large portion of the Harderian gland was removed, allowing the surgeon access to the eye muscle cone. Once the eye was gently pulled forward, the ocular muscles over the optic nerve were detached and held apart with a blunt hook so that only the retractor bulb muscle remained close to the optic nerve. Care was taken to maintain retinal perfusion during this maneuver. The retractor bulb muscle was then cut 2 mm behind the posterior portion of the eye and separated from the optic nerve.

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Histologic Preparation

Unless otherwise stated, all chemicals were obtained from Sigma (Deisenhofen, Germany) and were of the highest commercially available purity. After in vivo perfusion with heparinized Ringer’s lactate solution (0.2% Liquemin), the rats were perfused with a fixative containing 4% paraformaldehyde. The perfusion-fixed eyes were detached and further fixed in a solution containing 2% paraformaldehyde and 2% glutaraldehyde in 0.1 M sodium cacodylate buffer at pH 7.4 for 24 hours at 4°C. After having been extensively rinsed in buffer, the retinas were explanted, whole-mounted onto gelatin-coated slides, and stained using the cresyl violet method to label RGCs. The optic nerves were post-fixed in 2% osmium tetroxide and 0.1 M sodium cacodylate buffer for 2 hours at 4°C. They were then dehydrated and embedded in epoxy resin (Araldite) using a standard protocol. To rule out procedure-related optic nerve damage, semi-thin sections were stained for myelin and glial fibrillary acidic protein (GFAP). They were stained for myelin with 1% paraphenylenediamine (PPD) solution in methanol/isopropanol. Unchelated stain was cleared with ethanol. Staining for GFAP involved incubating the semi-thin sections with 0.5% H2O2 in phosphate-buffered saline (PBS) for 15 minutes and with 10% fetal calf serum (FCS) for 30 minutes at 20°C to block endogenous peroxidase activity and nonspecific protein binding. The specimens were then incubated overnight at 4°C with a primary rabbit anti-GFAP antibody (1:80; Sigma) followed by a secondary goat anti-rabbit antibody. Avidin-biotin-horseradish peroxidase complex was added for 1 hour at 20°C. The sections were then exposed to 3,3-diaminobenzidine (0.05 mg/ml) in PBS containing 1% H2O2 for 5 minutes. Between each step, the sections were washed 3 times in PBS. All incubations were performed in a humidified chamber. The slides were either left unstained or counterstained with hematoxylin. Negative controls were subjected to the same procedure without exposure to the primary antibody. All control stainings were negative.

**Histologic Analysis**

For quantitative analysis, each retina was divided into upper, upper lateral, lower lateral, lower, and medial sections. Three regions of interest (ROIs) (12,346 μm²) were defined in each section to accommodate possible differences in the neuronal response resulting from different axonal distances between the neuronal cell body and the site of axon damage. The central ROI was located at 1.2 mm, the intermediate ROI 2.4 mm, and the peripheral ROI 2.6 mm from the optic disc. The numbers and sizes of neurons in the RGC layers were determined by evaluating each ROI at a magnification of 900 times using a camera lucida, a digitizer tablet attached to a personal computer, and Bioquant System IV software (R&M Biometrics Inc., Nashville, TN). For each retina, the total number of neurons (N) was calculated according to the following formula:

\[
N = N_X \times (A_R \times 0.8556) \times ROI^{-1}
\]

where \(N_X\) is the mean number of neurons (averaged over the three ROIs), \(A_R\) is the size of the retina (in mm²), ROI is an area of 0.012346 mm², and 0.8556 represents a factor that was calculated to represent the portion of the RGC layer in Wistar rats that is covered by neurons and is not occupied by large intraretinal vessels (9).

A total of 50% of the neurons in the RGC layer were classified as RGCs, which project their axons centrally through the optic nerve. The other 50% of the neurons were amacrine cells, which do not send axons into the optic tract and are thus unaffected by optic nerve trauma (9). Neurons larger than 80 μm² in size are likely to represent RGCs, whereas neurons smaller than 80 μm² are likely to represent amacrine cells.
Cell counts obtained from all experimental groups were pooled, and the neurons were divided into several size classes at increments of 10 \( \mu \text{m}^2 \) to evaluate neurodegenerative changes in the RGC layer (Fig. 2).

For a morphological evaluation of the optic nerves, cross sections were prepared and stained for myelin with PPD. Because GFAP, an intermediate filament protein, is expressed by glial cells in response to injury, immunoreactivity to GFAP was qualitatively assessed. For measuring the cross-sectional area of the myelinated portion of the optic nerve, only nerves that conformed to the criterion of a perfect right-angular cross section were evaluated. At
a magnification of 900, the numbers of myelinated axons were counted in at least 10 30 × 30-μm ROIs at random in all areas using Bioquant System IV software. The total numbers of myelinated axons were then calculated for each optic nerve cross section.

### Statistical Analysis

Results are expressed as mean ± SEM. Depending on the distribution of data, differences between groups were analyzed using a one-way analysis of variance (ANOVA) or a one-way ANOVA on ranks. The parametric Student’s *t* test or the nonparametric Mann-Whitney *U* test was used post hoc to isolate specific differences. *P* < 0.05 was considered significant.

### RESULTS

#### Pupillomotor Function

Compared with the controls, no animal that underwent sham surgery or standardized intraorbital ONSF exhibited a relative afferent pupillary defect when a swinging flashlight test was performed before the operation, immediately after the operation, or before paraformaldehyde perfusion (30 days after surgery).

#### Histologic Retinal Findings

Figure 1 shows typical light microscopic images of cresyl violet–stained RGC layers that were obtained 30 days after ONSF or the sham operation. A computer-assisted quantitative analysis revealed that the total number of amacrine cells and RGCs in the RGC layer was significantly reduced by 7% after ONSF than after the sham operation (*P* < 0.05) (Table 1). In particular, 30 days after the interventions, the numbers of neurons larger than 80 μm² and smaller than 80 μm² were found to be significantly lower after ONSF than after sham surgery (*P* < 0.05). In contrast, there was no significant difference in the numbers of glial cells in the RGC layer between Group 1 (10,723 ± 1,053) and Group 2 (11,380 ± 2,360). A morphometric analysis showed that the RGCs were significantly (*P* < 0.05) smaller in Group 1 than in Groups 2 and 3 (Table 1).

The frequency distribution of neuronal sizes revealed a pronounced left-skewed histogram after ONSF, whereas the distribution was more homogenous in the control and sham operation groups, as indicated by the distinct frequency of neurons larger than 80 μm² (Fig. 2). However, ONSF did not substantially affect the distribution of RGCs and amacrine cells. In all study groups, the density of neurons decreased from central to peripheral retina, whereas the size of retinal neurons increased (Table 1, Fig. 2).
**Histologic Optic Nerve Findings**

Figure 1 shows optic nerve cross sections stained with PPD. Intensely stained myelin appeared as dark rings surrounding unstained cores (the axons themselves). A qualitative analysis showed that these fibers were clustered in fascicles, which were separated by lightly stained bands of connective tissue. Immunohistochemical staining revealed that GFAP was localized on glial intermediate filament bundles. There were no differences between groups 1 and 2 (Fig. 1). In addition, the axon count was comparable in all groups assessed (Table 1). After ONSF or sham surgery, the optic nerves exhibited a normal histomorphology.

**FIG. 2** Frequency distribution of neuron sizes at increments of 10 μm² in retinal ganglion cell (RGC) layers after optic nerve sheath fenestration (ONSF) (A; counts = 9,530, n = 12) and after sham surgery (B; counts = 8,622, n = 10). The RGC layers of unoperated and unexposed optic nerves (C; counts = 19,221, n = 22) served as controls. The lower portion of a bar represents the central region, the middle portion the intermediate region, and the upper portion the peripheral region of the retina. Note that the frequency distribution reveals a pronounced left-skewed histogram after ONSF.
Direct surgical damage to the optic nerve by ONSF was therefore ruled out.

**DISCUSSION**

This study reveals that ONSF caused atrophy and degeneration of RGCs and amacrine cells. The optic nerve itself appeared undamaged.

The significantly reduced total number of RGCs and amacrine cells in the absence of axonal loss cannot be explained solely by a degeneration of amacrine cells. Because amacrine cells are smaller than 80 \( \mu \text{m}^2 \), the degeneration of these smaller neurons would result in a right-skewed histogram for the frequency distribution of neuron sizes. Taking into account the observed left-skewed histogram, our results suggest that the ONSF procedure resulted in a distinct loss of amacrine cells and a marked shrinkage of larger RGCs. In a recent report using retrograde labeling (17), cell body shrinkage was shown to be the initial phase of RGC degeneration.

Exposure of the intraorbital optic nerve requires the eye to be carefully rotated to the side. RGC neurodegeneration, however, is unlikely to result from the pressure that was applied to the orbital content during the procedure. Repeated ophthalmoscopy revealed no disturbances of retinal perfusion during the period of surgical preparation. In addition, RGC neurodegeneration was not observed in those animals that underwent exposure of the intraorbital optic nerve. It is therefore likely that the incision into the leptomeningeal sheath of the optic nerve induced microvascular changes in the optic nerve that resulted in temporary retinal hypoperfusion, which could explain the degeneration of RGCs observed 30 days after the fenestration procedure. Choroidal infarction has been reported as a complication of ONSF (18).

Because ONSF was found to cause significant atrophy and degeneration of RGCs, the risks and benefits of ONSF should be taken carefully into account.

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Progressive Optic Neuropathy in Idiopathic Intracranial Hypertension After Optic Nerve Sheath Fenestration

Byron N. Wilkes, MD and R. Michael Siatkowski, MD

Abstract: A 16-year-old woman complaining of headache and declining vision in both eyes had papilledema, normal brain imaging, and a lumbar puncture showing a moderately high opening pressure (35 cm H₂O) and normal cerebrospinal fluid constituents. For a diagnosis of idiopathic intracranial hypertension (IIH), she was treated with acetazolamide and methylprednisolone, but vision worsened, so she underwent bilateral optic sheath fenestration (ONSF). Within the 1st postoperative week, vision had improved and papilledema was less prominent. However, by the 14th postoperative day, vision had worsened and headache persisted. Lumbar puncture showed a very high opening pressure (65 cm H₂O), so she underwent ventriculoperitoneal shunting. Although there was a slight initial improvement in vision, it eventually declined further. This case emphasizes that ONSF may yield initial improvement in vision and reduction in papilledema yet not prevent eventual visual loss in IIH. Whether the visual loss in this patient resulted from persistently elevated intracranial pressure after ONSF or was prefigured before ONSF occurred is unresolved. It is a reminder that patients with IIH must be monitored carefully after ONSF. If there is a suggestion of further visual loss, shunting should be considered if intracranial pressure is high.

A 16-year-old overweight African American woman presented with headache and decreased vision in both eyes for 2 weeks. Best-corrected visual acuity was 20/25 in the right eye and 20/40 in the left eye. Automated static perimetry showed generalized depression with enlarged blind spots bilaterally (Fig. 1). She identified 13/14 Ishihara plates with the right eye and 12/14 with the left eye. Ophthalmoscopy revealed marked optic disc edema bilaterally with moderate hemorrhage.

Results of brain MRI were normal. Lumbar puncture revealed an opening pressure of 35 cm H₂O with normal chemistry and no cells. Idiopathic intracranial hypertension (IIH) was diagnosed, and she was treated with 500 mg oral acetazolamide twice daily along with intravenous methylprednisolone 125 mg every 6 hours.

Five days after starting therapy, the patient complained of worsening headaches and declining vision. Visual acuity remained 20/25 in the right eye but had worsened to 20/60 in the left eye. Color vision had declined in both eyes. Visual field testing showed worsening defects (Fig. 2).

Repeat lumbar puncture revealed an opening pressure of 65 cm H₂O (obtained by connecting 2 manometers). Bilateral optic nerve sheath fenestration (ONSF) was performed. The optic nerves were approached via a medial trans-conjunctival incision after securing and detaching the medial rectus muscles. The optic nerves were dissected from the surrounding connective tissue and a rectangular window was created in the optic nerve sheath. A large gush of cerebrospinal fluid (CSF) was noted to flow into the orbit immediately after incision of the optic nerve sheath on both sides. There were no intraoperative complications.

On the 4th postoperative day, visual acuities were 20/25 in the right eye and 20/40 in the left eye. Color vision had recovered to 14/14 Ishihara plates bilaterally. Visual fields had improved (Fig. 3). The optic discs were less swollen, and spontaneous venous pulsations were noted for the first time.

Fourteen days later, the patient complained of worsening headache and declining vision. Best-corrected visual acuities were 20/100 in both eyes. Color vision had also declined. Visual fields showed large bilateral central scotomas (Fig. 4). Ophthalmoscopy revealed complete resolution of
papilledema without optic disc pallor in both eyes. Spontaneous venous pulsations were present in both eyes.

Results of brain MRI were normal. Lumbar puncture revealed an opening pressure of 65 cm H$_2$O. The patient underwent ventriculoperitoneal (VP) shunting.

Two weeks after successful shunting, visual acuity had improved to 20/40 in the right eye and 20/80 in the left eye. Ophthalmoscopy showed no change in the appearance of the optic nerves. Visual fields showed a decrease in the size of the central scotomas in both eyes. Color vision had improved to 13/14 plates in the left eye.

Five weeks later the patient complained of a further decrease in vision. Headache was no longer present. Best-corrected visual acuities were 20/200 in the right eye and 20/200 in the left eye. Color vision was markedly reduced at 1/7 and 2/7 color plates in the right and left eyes, respectively. Visual field testing revealed bilateral central scotomas (Fig. 5). Ophthalmoscopy now revealed temporal optic disc pallor and nerve fiber layer dropout in the papillomacular bundle of both eyes.

At the last clinical visit, 10 months after the VP shunt, the patient’s visual acuity was 20/150 in the right eye and 20/125 in the left eye. Visual fields were unchanged. Ophthalmoscopy showed moderate optic disc pallor bilaterally.

**DISCUSSION**

Our patient is reported because of her unusual clinical course after ONSF and VP shunting. After ONSF, visual function briefly improved initially, and optic disc edema resolved. But visual deterioration soon set in, and intracranial pressure (ICP), as measured by lumbar puncture, was very high. After VP shunting, headache resolved but vision continued to worsen, and optic disc pallor eventually appeared. Visual fields had high reliability indices and seemed to be consistent in confirming failing vision despite the interventions.

This phenomenon is unusual but has been reported previously. Mauriello et al (1) reported that 1 of 5 patients who had undergone ONSF for IIH had initial improvement in visual acuity but later required a lumboperitoneal (LP) shunt for worsening vision 3 days after the ONSF. In that report, however, there was no mention of the pre-shunt level of ICP or an explanation for the visual loss.

Previous studies have suggested that ONSF can lower the pressure within the optic nerve sheath and the intracranial space by allowing CSF flow through the fenestration (2,3). Long-term ICP lowering, however, would require a constant flow of CSF between the...
intracranial and optic sheath subarachnoid spaces (SASs), a phenomenon that may not occur in patients with IIH. For example, Killer et al (4) noted that CSF flow may not be bidirectional within the optic nerve sheath in individuals with IIH. Their work suggests a paucity of CSF flow from the intracranial SAS to the SAS of the optic nerve sheath in patients with IIH, evidenced by the presence of continued papilledema in some patients after successful VP shunting. This CSF flow impedance results in abnormal flow in the orbital segment of the nerve (4). These authors suggest that the anatomical narrowing of the intracanalicular optic nerve sheath SAS to a potential space could be a contributing factor. Perhaps the compartmentalization is due to changes within the dura and arachnoid related to inflammation and subsequent fibrosis in the SAS (4). There is also evidence that compartmentalization of the optic nerve SAS leads to the accumulation of biologically active molecules, which could lead to local cell apoptosis (5). It is unclear where the primary site of impedance lies, but it could be anywhere posterior to the site of ONSF. Although flow in the optic canal has not been reliably measured, the narrowed potential space there leads to the speculation that this is at least a contributing factor.

The compartmentalization described by Killer et al (4) may explain what happened in our patient. Notably, however, Killer et al (4) described persistent papilledema not after ONSF, but after VP shunt, indicating an impedance of CSF flow from the optic nerve sheath to the intracranial space. Our patient’s persistently elevated ICP after ONSF suggests the possibility of a paucity of flow from the intracranial SAS to that of the optic nerve. Thus, ONSF may not always be able to decompress the elevated ICP affecting the intracranial and canalicular portions of the optic nerve. Shunting may not be able to reduce the elevated ICP on the optic nerves if this compartmentalization prevents fluid flow from the optic nerve SAS to the intracranial SAS.

The ICP in IIH has been reported to range from 20 to 50 cm H₂O with a mean of 34.4 cm H₂O (6). A smaller series did include a patient with an opening pressure of 65 cm H₂O; however, this level of ICP is exceedingly rare (7). This persistently very high pressure after ONSF may explain why the patient continued to have visual loss despite adequate decompression of the optic nerve heads. There are other explanations for this patient’s progressive visual loss after surgical intervention. Poor outcomes in IIH are higher in pubescent individuals and in African Americans (8,9). The progressive visual loss may have been the result of a process well underway by the time ONSF occurred.

This case suggests that it is important to recognize that patients with IIH and highly elevated ICPS may not be adequately treated after ONSF even if it initially results in a reversal of visual loss and papilledema. In such instances, ICP must be measured, either by lumbar puncture or by direct intracranial monitoring. If it is still elevated, prompt shunting should be considered.

REFERENCES


Complete Bilateral Ophthalmoplegia Resistant to Caloric Stimulation in Bilateral Paramedian Midbrain-Thalamic Infarction

Miguel Angel Tola-Arribas, MD, Alejandro Vara-Castrodeza, MD, and Juan Ernesto Alonso-Santor, MD

Abstract: A 79-year-old woman who developed bilateral paramedian midbrain-thalamic infarction manifested complete bilateral ophthalmoplegia resistant to caloric stimulation, indicating impairment of the vestibulo-ocular reflex (VOR). Previous reports have mentioned this phenomenon but have not explicitly reported the results of caloric testing. Why a lesion apparently confined to the upper brainstem should produce impairment of the horizontal VOR remains unexplained.


Oclusion of the midbrain and thalamic perforating branches of the posterior cerebral arteries in their proximal segment, called the “top of the basilar” syndrome, is known for its wide variety of clinical manifestations (1). Bilateral complete ophthalmoplegia has, however, been rarely described (2–7). None of the reports includes information about eye movement responses to caloric testing or passive head movement. We describe a patient with acute complete bilateral ophthalmoplegia due to a bilateral paramedian midbrain-thalamic infarction in whom such testing produced no improvement in eye movements, indicating that the vestibulo-ocular reflex (VOR) pathway was impaired. Why a lesion apparently limited to the upper brainstem should impair the horizontal VOR pathway remains unexplained.

CASE REPORT
A 79-year-old woman with a history of hypertension and bilateral carotid endarterectomy suddenly became unresponsive to noxious stimuli. She also had complete bilateral ptosis. Her eyes were in the primary position, and there were no spontaneous eye movements. Pupils measured 8 mm in dim illumination and did not constrict to direct light. Caloric testing with cold water or with passive head movement failed to elicit any eye movement. Corneal and gag reflexes were normal. There were bilateral spontaneous movements of all four extremities and normal deep tendon reflexes. There was no Babinski reflex. Based on these findings, a toxic process was initially suspected.

Results of electrocardiography were normal. Brain CT showed mild signs of small vessel ischemic white matter disease. Brain MRI performed 2 days after symptom onset demonstrated acute bilateral paramedian midbrain-thalamic infarction (Fig. 1A–D). MRA images showed complete basilar artery occlusion (Fig. 1E–F).

Over the following days, she remained unresponsive, and her bilateral ophthalmoplegia and mydriasis remained unchanged. She died of pneumonia a few weeks after presentation. No autopsy was performed.

DISCUSSION
This patient had occlusion of the arterial supply of the paramedian thalamus and midbrain, an infrequent and grave variant of the top of the basilar syndrome that manifests clinically with a wide variety of ocular motor, sleep-wake cycle, alertness, behavioral, and motor abnormalities (8,9). Despite imaging evidence of basilar artery thrombosis, no pontine clinical or imaging abnormalities were observed. However, based on caloric testing, the VOR pathway to stimulate abduction, which does not course through the midbrain or thalamus, was absent. This phenomenon is unexplained.

Patients with complete ophthalmoplegia in this setting have generally died within days of onset. Survivors have demonstrated improvement of abduction within a few days (2).
REFERENCES


**FIG. 1.** Diffusion-weighted (A), fluid-attenuated inversion recovery (B), T2 coronal (C), and T2 axial (D) MRI sequences show acute bilateral paramedian midbrain-thalamic infarction. Coronal (E) and sagittal (F) MRA time-of-flight images show occlusion of the middle and distal basilar arteries (arrowheads).
Ocular Tilt Reaction as a Delayed Complication of Deep Brain Stimulation for Parkinson Disease

Santiago Ortiz-Pérez, MD, Bernardo Sánchez-Dalmau, MD, Juan Molina, MD, Alfredo Adán, PhD, Santiago Candela, MD, and Jordi Rumia`, MD

Abstract: A 57-year-old-man treated with deep brain stimulation (DBS) of both subthalamic nuclei for advanced Parkinson disease developed a brain hemorrhage near the site of one of the DBS electrodes 9 months after implantation. The hemorrhage caused vertical diplopia from skew deviation. Examination also disclosed evidence of ipsiversive binocular torsion and a right head tilt, constituting an ocular tilt reaction (OTR). Fourteen months later, he was still symptomatic from diplopia. An OTR has not previously been reported as a delayed complication of DBS.


In patients with advanced Parkinson disease (PD), deep brain stimulation (DBS) of the subthalamic nucleus (STN) has been shown to improve motor function and decrease the need for pharmacologic treatment (1–3). DBS is able to modulate the target region in a reversible and adjustable fashion in contrast to the irreversible and destructive nature of thalamotomy and pallidotomy. With the development of DBS technology and stereotactic neurosurgical techniques, DBS has become a promising therapy not only for PD but also for other disabling movement and neuropsychiatric disorders such as Tourette syndrome, obsessive-compulsive disorder, and refractory depression (4).

The most frequent side effects documented in relation to DBS are local brain hemorrhage, infection, ischemia, device misplacement, or battery migration (5). Aggravated dyskinesias, seizures, and psychiatric disorders have also been reported (5,6). Intracerebral hemorrhage generally occurs in the perioperative period but delayed hemorrhage has been described (7). A history of hypertension and PD has been reported as a predictive factor (8).

The ocular tilt reaction (OTR), a sign of vestibular dysfunction in the roll plane, is characterized by the triad of ocular torsion, skew deviation (SD), and head tilt (9–11). SD is a vertical strabismus caused by damage to the otolithic-ocular reflex pathway and is associated with abnormal ocular torsion. We describe an OTR as a late complication of DBS. Although conjugate gaze deviation has been reported after STN DBS (12,13), we are unaware of previous reports of OTR in this context.

CASE REPORT

A 54-year-old man with an 8-year stable course of PD developed motor oscillations with on/off phases uncontrolled by full doses of levodopa, amantadine, and selegiline. Bilateral DBS of the STN was therefore performed using a surgical procedure reported previously (14). In the immediate postoperative period, the patient developed somnolence, disorientation, left hemiparesis, ataxia, and a left Babinski reflex. CT showed an intracerebral hemorrhage adjacent to the right electrode (Fig. 1A). Three weeks later, the area of hemorrhage had decreased (Fig. 1B), and all clinical deficits had resolved.

DBS provided substantial improvement in the motor signs of PD and in the activities of daily living in this patient, as it has in previously reported patients (15). Motor fluctuations and the dose requirements of dopaminergic medication declined, and there were no dyskinesias or other side effects.

However, 9 months after implantation of electrodes, the patient suddenly developed vertical diplopia and headache. Our examination disclosed a 20 prism-diopter left hypertropia in primary gaze with a right head tilt (Fig. 2). Fundus photography showed a left eye incyclotorsion with perhaps a right eye excyclotorsion (Fig. 3) (16,17). On right gaze, the hypertropia was 8 prism-diopters, and on left gaze it was 30 prism-diopters (Fig. 2). There was no motor deficit, sensory impairment, ataxia, or change in consciousness. Brain CT revealed a right subthalamic hemorrhage in the same place as the postoperative hemorrhage (Fig 1C).
The ocular motor findings were interpreted as constituting an ipsiversive OTR, including ocular torsion toward the side of the lesion and SD.

No intervention occurred. Fourteen months later, the head tilt and left hypertropia had substantially improved, but the patient still had intermittent diplopia and tilt of the visual environment from the OTR.

**DISCUSSION**

We have described a patient who developed a delayed right subthalamic hemorrhage near the site of one of the DBS electrodes. It produced a persistent OTR from which the patient remained symptomatic. The hemorrhage probably resulted from damage to cerebral blood vessels caused by the DBS procedure and the repeated stimulation in the area of the electrode.

An OTR is usually attributed to an imbalance in the otolith-ocular and otolith-neck reflexes that are part of a phylogenetically ancient righting response to a lateral tilt of the head. These pathways subserve the vestibulo-ocular reflex (VOR) (18). The primary functions of the VOR are to maintain eye position and stable fixation during head movements (9,10,19). Most OTRs are due to a brainstem or cerebellar lesion (5,20).

The OTR is characterized by perception of tilt of the visual environment, ocular torsion, SD, and a head tilt. The SD is usually comitant but can be incomitant, as in our patient. A binocular conjugate ocular torsion and paradoxical head tilt (the head and superior pole of both eyes are rotated toward the hypotropic eye) are typically present (9). Unilateral cerebellar or pontomesencephalic lesions affecting the interstitial nucleus of Cajal (INC) or the medial longitudinal fasciculus typically cause contraversive deviation (the contralateral eye is lower). Peripheral vestibular and pontomedullary lesions typically cause ipsiversive deviation (the ipsilateral eye is lower). Thalamic lesions may cause either contraversive or ipsiversive tilt of the subjective visual vertical (9,10,18).

The OTR is usually attributed to an imbalance in the otolith-ocular and otolith-neck reflexes that are part of a phylogenetically ancient righting response to a lateral tilt of the head. These pathways subserve the vestibulo-ocular reflex (VOR) (18). The primary functions of the VOR are to maintain eye position and stable fixation during head movements (9,10,19). Most OTRs are due to a brainstem or cerebellar lesion (5,20).

The lesion in our patient, which caused an ipsiversive OTR, was located in the right subthalamic region, perhaps affecting the right INC. In humans, mesodiencephalic lesions involving the INC produce a contraversive OTR if the lesion is inhibitory and an ipsiversive OTR if the lesion is excitatory (9,20). The bleeding in our patient presumably produced an excitatory injury of the INC.

The OTR has been described in association with acute unilateral vestibular lesions (21), posterior fossa tumors (9), multiple sclerosis (9), head trauma (9), epileptic
disorders (22), and neurosurgical procedures (23). Other isolated documented causes are increased intracranial pressure (9), central nervous system malformations (9), infections (24), cardiac catheterization (25), Creutzfeldt-Jakob disease (9), polyarteritis nodosa (26), and multifocal leukoencephalopathy (9).

As far as we know, OTR has not previously been reported as a complication of DBS. With the increasing use of such interventions, this possible complication should be recognized, especially because of the participation of the INC in the physiopathology of SD and OTR and its close proximity to the placement of electrodes for DBS treatment of PD.

REFERENCES


FIG. 3. Conjugate ocular torsion as evidenced by fundus photography. With the patient in primary gaze position, there is a 15° extorsion of the right eye (A) and an 8.2° intorsion of the left eye (B) based on the relationship of the fovea to the optic disc.
Intracranial Malignancies Occurring More Than 20 Years After Radiation Therapy for Pituitary Adenoma

Wen Ying Wu-Chen, MD, Dina A. Jacobs, MD, Nicholas J. Volpe, MD, Joseph O. Dalmau, MD, PhD, and Mark L. Moster, MD

Abstract: A 37-year-old woman developed a left third cranial nerve palsy 28 years after radiation for a nonsecreting pituitary adenoma. Imaging disclosed a left parasellar mass and a midbrain/pontine signal abnormality. Biopsy of the parasellar mass revealed a malignant sarcoma. The brainstem abnormality was presumptively diagnosed as a malignant glioma. A 63-year-old man developed a malignant astrocytoma of the left optic nerve and chiasm 23 years after partial excision and radiation of a nonsecreting pituitary adenoma. Both patients died of their malignancies. Although secondary malignancies have been described in this setting, such long latencies have not been reported.

(Radiation therapy is a mainstay of treatment for many nervous system tumors. Among them are pituitary adenomas, which may be treated with fractionated radiation or single-dose radiosurgery to control tumor growth and hormone hypersecretion (1). Complications of radiotherapy include neurovascular damage, radionecrosis, progressive fibrosis, deletion of oligodendroglial and neural stem cell populations, alterations in cytokine expression, and disruption of cellular DNA (2).

Radiation-associated tumors are a late complication 2. They may arise within the brain, dura, cranial bones, or spinal and peripheral nerves. We present two patients who developed secondary malignancies 23 and 28 years after radiotherapy. Such long latencies have not been reported previously.

CASE REPORTS

Case 1
A 37-year-old woman had a pituitary adenoma at age 9 years. The tumor was resected and the final pathologic identification was a nonsecreting adenoma. After the surgery, she underwent a course of radiation therapy at an unknown dose with resolution of a visual field defect and no evidence of optic neuropathy at that time. She had a recent diagnosis of hypertension.

Twenty-eight years later, she developed left upper lid ptosis and diplopia. At the onset of diplopia, examination elsewhere was notable for a dilated and sluggishly reactive left pupil, left upper lid ptosis, and complete left adduction, supraduction, and infraduction deficits. The findings were considered to be reflective of a left third cranial nerve palsy. Brain MRI was interpreted as showing abnormal T2 signal biaterally in the pons extending to the medulla, believed to be consistent with chronic ischemic change, inflammation, or demyelination. Lumbar puncture revealed a normal opening pressure and normal constituents, and results of a cerebral angiogram were also normal.

We examined her 8 months later. Visual acuity was 20/20 in both eyes, visual fields were full to confrontation, and color plates were fully identified. There was no afferent pupillary defect. Results of dilated ophthalmoscopy were unremarkable. There was a complete left third cranial nerve palsy with a mydriatic pupil that did not constrict to direct light. The remainder of the neurologic examination was normal.

Repeat brain MRI (Fig. 1) revealed focal enhancement in the left parasellar region and in the left midbrain at the site of exit of the left third cranial nerve. The MRI T2 signal change in the caudal brainstem described on the earlier MRI was still present.

Magnetic resonance spectroscopy showed elevation of choline with respect to creatinine and depression of...
$N$-acetylaspartate (NAA) in the parts of the lesion involving the pons and midbrain. Portions of the lesion also demonstrated elevated lactate. The appearance was considered consistent with a primary neoplasm of the brainstem. She was given a presumptive diagnosis of a post-radiation brainstem glioma and treated with temozolomide. The parasellar lesion was biopsied with the final pathologic analysis revealing a highly malignant sarcoma. Despite receiving several cycles of intravenous cyclophosphamide, vincristine, and doxorubicin over 8 weeks, the brainstem lesion progressed and she died a few months later.

**Case 2**

A 62-year-old man had undergone resection of a nonsecreting pituitary adenoma via a left frontal craniotomy at age 39, followed by 5,400 rads of radiotherapy. Visual function normalized at that time, and periodic examinations and brain imaging revealed no evidence of tumor recurrence.

Twenty-three years after radiotherapy, he awoke with painless blurred vision in the left eye. Examination elsewhere disclosed visual acuities of 20/20 in both eyes with a left afferent pupillary defect, a nasal step defect on Humphrey visual field testing, and a swollen left optic disc. An initial diagnosis of nonarteritic anterior ischemic optic neuropathy (NAION) was made, but later review of a brain MRI showed that the left optic nerve was enlarged (Fig. 2A).

He came to our attention when, over the next several weeks, visual acuity worsened in the left eye as did the left eye visual field defect and optic disc edema. Cerebrospinal fluid evaluation revealed 7 white blood cells (90% lymphocytes and 10% monocytes), 9 red blood cells,
<table>
<thead>
<tr>
<th>Publication</th>
<th>Hormonal Secretion by Initial Tumor</th>
<th>Age at Treatment of Initial Tumor (years), Sex</th>
<th>Radiation Dose (Gy)</th>
<th>Latency (years)</th>
<th>Clinical Presentation</th>
<th>Secondary Tumor</th>
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<td>Terry et al, 1959 (23)</td>
<td>None</td>
<td>26, F</td>
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<td>NA</td>
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<td>None</td>
<td>26, M</td>
<td>36 + 14 (5 months later)</td>
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<th>Publication</th>
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<th>Latency (years)</th>
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<td>50</td>
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<td>Ptosis and complete ophthalmoplegia</td>
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<td>Pieterse et al, 1982 (45)</td>
<td>None</td>
<td>48, M</td>
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<td>Progressive visual loss and recurrent bitemporal hemianopsia</td>
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<td>None</td>
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<td>PRL</td>
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<td>NA</td>
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<td>GH</td>
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<td>GH</td>
<td>26, M</td>
<td>66</td>
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<td>Memory loss, lethargy, right-sided weakness, right homonymous hemianopsia, and optic atrophy</td>
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<td>Shapiro et al, 1989 (26)</td>
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<td>45 + 50 (12 years later)</td>
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<td>Seizures, right seventh cranial nerve palsy, right hemiparesis, dysarthria</td>
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<td>Al-Meffly et al, 1990 (18)</td>
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<td>32, F</td>
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<td></td>
<td>GH</td>
<td>34, F</td>
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<td>PRL</td>
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<td>8</td>
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<td>Publication</td>
<td>Hormonal Secretion by Initial Tumor</td>
<td>Age at Treatment of Initial Tumor (years), Sex</td>
<td>Radiation Dose (Gy)</td>
<td>Latency (years)</td>
<td>Clinical Presentation</td>
<td>Secondary Tumor</td>
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<td>Gnanalingham et al, 2002 (4)</td>
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<td>Loeffler et al, 2003 (24)</td>
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<td>54</td>
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*Clinical diagnosis.  
NA, not available; GH, growth hormone; PRL, prolactin.
29 mg/dl of protein, and negative VDRL, acid-fast bacilli, cryptococcal antigen, cultures, and cytology. He underwent optic nerve biopsy via a frontotemporal craniotomy. The pathologic analysis revealed inflammatory changes with many mononuclear cells.

Visual acuity in the left eye transiently improved after treatment with corticosteroids, but over the next 8 months it gradually deteriorated to finger counting. Repeat brain MRI showed an enhancing mass that extended inferiorly into the sella and superiorly into the left frontal lobe (Fig. 2B). A craniotomy revealed tumor emanating from the optic nerve and lateral aspect of the optic chiasm. The exophytic portion of the tumor was removed, and pathologic analysis revealed an anaplastic astrocytoma. Despite treatment with chemotherapy, visual acuity deteriorated to no light perception, the tumor grew, and the patient died 7 years after presentation.

**DISCUSSION**

We have presented two cases of presumptive radiation-induced tumors occurring long after radiotherapy for pituitary adenoma. The first patient developed a para-sellar sarcoma and a presumed brainstem glioma 28 years after radiotherapy; the second patient developed a malignant astrocytoma of the optic nerve and chiasm 23 years after radiotherapy. Both patients died of their malignancies despite chemotherapy. The latencies are long, but we presume that the radiation caused these malignancies, given that they would be unusual spontaneous occurrences, they lay within the radiation field, and they developed in patients without an obvious genetic predisposition to cancer (3).

Although third cranial nerve palsy has been reported along with other visual findings in a radiation-associated sarcoma (4) in the pituitary fossa with spread to the chiasm, cavernous sinuses, and nasopharynx, a presentation with isolated third nerve palsy has not been previously described. The second patient was also unusual in having an acute onset of vision loss and a swollen optic disc, features that initially suggested NAION. In that patient, the first biopsy showed only inflammatory cells, leading to a diagnosis of optic neuritis.

Sarcomas are the most commonly reported intracranial tumors presumed to be radiation-induced, followed by gliomas and meningiomas (Table 1, 4–28). The latency period ranges from 1 year to >30 years (4–28). In a review of brain tumors after radiation for pituitary adenomas, Brada et al (19) found that 11 (2.4%) of 426 patients developed a second intracranial tumor. Of the 426 patients, 76% had received 40–50 Gy in 20–30 fractions; 23% had received ≥50 Gy. Based on that study, the cumulative likelihood of developing a secondary tumor was 2.0% within the first 10 years and 2.4% within 20 years, with an overall relative risk of 10.5 compared with that of the general population (19,20). The authors noted a median latency of 7.0 years (range 1–22 years) for glioma, 9.7 years (range 5–27 years) for sarcoma, and 13.8 years (range 7–34 years) for meningioma (19,20). Tsang et al (21) reported 4 cases of gliomas arising after radiation therapy for pituitary adenoma with latencies between 8 and 15 years. The malignancies in our 2 patients were identified much later. There is a strong correlation between radiation dose and the risk of development of a secondary tumor, with the relative risk approaching 20 after doses of 2.5 Gy or higher (29). Higher doses are associated with shorter latency periods (30,31).

**REFERENCES**


Ocular Motor and Imaging Abnormalities of Midbrain Dysfunction in Osmotic Demyelination Syndrome

Kristen M. Hawthorne, MD, Christopher J. Compton, MS, Michael S. Vaphiades, DO, Glenn H. Roberson, MD, and Lanning B. Kline, MD

Abstract: After rapid correction of severe hyponatremia, a 36-year-old man developed osmotic demyelination syndrome (ODS), manifested neurologically by impaired cognition, extremity weakness, bilateral third cranial nerve palsies, and gaze-evoked upbeat and rotary nystagmus. Brain MRI showed restricted diffusion in the rostral midbrain and temporal and parietal lobes but not in the pons. Over several weeks, all neurologic and imaging deficits resolved. This is the first report to document ocular motor abnormalities associated with midbrain dysfunction in ODS.


Osmotic demyelination syndrome (ODS) describes a spectrum of neurologic symptoms resulting from central nervous system demyelination precipitated by rapid correction of hyponatremia. ODS was first described in 1959 by Adams et al (1) and labeled central pontine myelinolysis (CPM) after a symmetric demyelinating lesion of the central pons was noted post mortem in alcoholics and malnourished individuals. In 1962, another subset of patients with ODS was described as having autopsy findings of demyelinating lesions in the external and internal capsules and anterior commissure, so-called extrapontine myelinolysis (EPM) (2). Subsequent reports (3,4) have documented that EPM can occur in the cerebellum, cerebrum, thalamus, subthalamic nucleus, hypothalamus, hippocampus, corpus callosum, mammillary, medial, and lateral geniculate bodies. A few reports have even documented midbrain involvement (4–6). Most reports document EPM and CPM together, but on occasion EPM may develop without CPM.

CASE REPORT

A 36-year-old man enrolled in a 3-week survival training program held outdoors during the summer. On the 5th day of intensive physical activity, he reported feeling ill despite frequent hydration. On arrival to the emergency department, the patient was unresponsive, had a grand mal seizure, and was found to be in pulmonary edema. Mechanical ventilation was started, and the patient was found to have a serum sodium level of 114 mmol/L (normal: 135–145 mmol/L). He was actively rehydrated with a rapid correction of electrolytes. On the 2nd hospital day, the patient developed a fever to 102F, was noted to have pulmonary consolidation on chest x-ray, and was given broad-spectrum antibiotics. The serum sodium level at that time was 119 mmol/L. On the 3rd day of hospitalization, he became afebrile and was extubated. Although his pulmonary status improved, he remained neurologically impaired. He had bilateral upper and lower extremity weakness, slurred speech, and slow mentation. His serum sodium level was now 142 mmol/L, and brain MRI revealed areas of restricted diffusion in the rostral midbrain, as well as the medial temporal, parietal, and subfrontal cortex bilaterally (Fig. 1). These findings were confirmed on T2 and FLAIR sequences (Fig. 2). There were no signal abnormalities in the pons (Fig. 3).

By the 12th hospital day, the patient was alert although his speech and mentation remained slow. Neuro-ophthalmologic examination demonstrated a visual acuity of 20/30 in the right eye and 20/20 in the left eye. Color vision was normal, and visual fields were intact to confrontation. Pupils were equal in size and briskly reactive to light without relative afferent pupillary defect. There was bilateral ptosis and a prominent exotropia. Eye movements showed reduced supraduction, infraduction, and adduction of both eyes (Fig. 4). In upgaze the patient developed...
upbeat nystagmus with a rotary component. Results of anterior and posterior ocular segment examinations were unremarkable.

Over the next 17 days, there was complete resolution of ptosis and ocular motor abnormalities. One month after hospitalization, the patient was noted to have only occasional square-wave jerks in primary gaze. His overall clinical condition continued to improve and with intensive physical therapy he was able to walk without assistance. Cognition and speech returned to normal. Results of brain MRI on the 32nd day after hospitalization were normal.

**DISCUSSION**

We have described a patient with ODS whose case is unusual in manifesting the clinical and imaging abnormalities of midbrain rather than pontine dysfunction. Although pontine and extrapontine clinical and imaging manifestations are widely documented in ODS, ocular motor abnormalities have been poorly described. Zegers de Beyl et al (7) reported ocular bobbing, limited abduction of the left eye, and impaired caloric testing for horizontal eye movements in a patient with CPM. Other descriptions in patients with both CPM and EPM include “pupillary abnormalities” (5), “pupillary and oculomotor abnormalities” (2), and “abnormalities of saccades without palsy” (8). We believe our patient manifested partial bilateral third cranial nerve palsies due to demyelinating lesions within the midbrain. In all likelihood, the fascicular portion of the third cranial nerve was affected. Pupil-sparing third cranial nerve palsies have been well documented with involvement of the fascicular portion of the nerve (9–12). Gaze-evoked upbeat nystagmus with a rotary component may have been due to concurrent involvement of the rostral interstitial nuclei of the medial longitudinal fasciculus (riMLF) bilaterally.

**FIG. 1.** A. Axial diffusion MRI demonstrates areas of increased signal bilaterally in the medial temporal lobes, subfrontal cortex, and rostral midbrain. B. Apparent diffusion coefficient map demonstrates hypointense signal in corresponding areas, consistent with restricted diffusion.

**FIG. 2.** A. Axial FLAIR MRI reveals areas of hyperintense signal that correspond to those seen on diffusion imaging (Fig. 1). B. Coronal FLAIR MRI demonstrates bilateral rostral midbrain hyperintense signals (arrows).
An understanding of the pathogenesis of ODS requires review of the physiologic changes occurring in acute and chronic hyponatremia. In the acute setting, when serum sodium decreases, water flows across the blood-brain barrier into relatively hypertonic brain cells, resulting in brain swelling. To counter this, a compensatory hydrostatic pressure mechanism forces interstitial fluid rich in inorganic ions such as sodium and potassium into the cerebrospinal fluid and ultimately back into the serum. Over the next 24–48 hours, brain cells pump out organic osmoles such as taurine and glutamine (2,13). At this point, brain cells have lost both inorganic ions and organic osmoles to reach an isotonic state and maintain cellular volume.

With correction of hyponatremia, there is a rapid increase of inorganic ions in serum, which now becomes relatively hypertonic to brain cells. This phenomenon leads to a shift of water out of cells with subsequent cell shrinkage. To prevent this, cellular tonicity must increase, requiring a reaccumulation of inorganic ions and organic osmoles. Damage occurs because the rate of these 2 protective mechanisms is slower than the rise in serum tonicity. Cell shrinkage precipitates cell death, particularly of oligodendrocytes, leading to demyelination. This osmotic stress probably triggers apoptosis, leading to further cell loss (2,13,14).

The classic finding in CPM is a hyperintense “trident-shaped” central pontine abnormality seen on T2 and FLAIR imaging (15,16), but this finding typically lags behind the clinical manifestations of ODS (17,18). With conventional MRI pulse sequences, myelinolytic lesions may not be detected within the first 2 weeks of onset. Indeed, imaging later in the clinical course has been advocated to confirm the diagnosis (18,19).

Diffusion-weighted imaging (DWI) and FLAIR sequences have demonstrated additional sites of involvement in EPM (20,21), including the cerebellum, cerebral cortex, thalamus, and external capsule. To our knowledge, however, there are no other reported cases of midbrain involvement detected with neuroimaging in the absence of pontine involvement. DWI has allowed earlier detection of brain lesions, probably because this technique is highly sensitive to the motion of intraparenchymal water, which is altered in ODS (17,18). DWI abnormalities have been detected early in the course of ODS without corresponding signal abnormalities on T1, T2, or FLAIR images (18). These changes may persist for 3 weeks (17).
The precise mechanism of these early signs of restricted diffusion in ODS remains to be clarified (17,18,21,23). It may be that in the hypernatremic state, water shifts from the extracellular to the intracellular space. The decrease in free water in the extracellular space, combined with the trapping of water in cells, may lead to restricted diffusion. Although restricted diffusion generally represents cytotoxic edema, evidently in ODS it does not, as many patients, including ours, make full neurologic recovery.

Treatment of ODS is aimed at prevention. Despite numerous published recommendations regarding correction of hyponatremia, there are no universally accepted guidelines (2). Standard practice is that hyponatremia be corrected slowly. Even after cessation of treatment, serum sodium levels can continue to rise for up to 2 days. With this in mind, it is recommended that sodium correction be ceased once neurologic symptoms have abated or the serum sodium level has increased by 10% (24).

Advances in fluid replacement guidelines and neuroimaging techniques have led to improved prognosis of patients with ODS. In general, approximately one third of patients progress to complete recovery, one third are left with mild neurologic deficits, and one third are left with severe neurologic impairment (25). Therefore, early diagnosis and proper treatment are critical in obtaining a good outcome in patients with ODS.

REFERENCES
Perineural Spread of Cancer Along the Three Trigeminal Divisions

Kara F. Warden, MD, Hemant Parmar, MD, and Jonathan D. Trobe, MD

Abstract: Perineural spread of head and neck cancers is a well-documented phenomenon, but the diagnosis is often delayed due to lack of familiarity with clinical manifestations, anatomy of the head and neck, and imaging signs. We present single cases of perineural spread along each of the 3 divisions of the trigeminal nerve in which the perineural spread was initially overlooked. Although perineural spread is often associated with a poor prognosis, earlier detection may improve outcome.


Perineural spread of cancer refers to the noncontiguous antegrade or retrograde extension of tumor cells along the tissues of the nerve. In head and neck cancers, it occurs in 2.5%–5% of patients (1). The second and third trigeminal nerve divisions and the facial nerve are most often involved (2,3). The cancers are usually adenoid cystic or squamous cell carcinoma, but any head and neck cancer can spread via this mechanism (2,4).

We present the clinical and imaging findings of single cases demonstrating perineural spread along the first (V1), second (V2) and third (V3) trigeminal divisions. In none of these patients was the perineural spread initially recognized.

CASE REPORTS

Case 1
A 74-year-old man was treated with cryoablation for presumed squamous cell skin carcinoma above the left brow. Five weeks later he developed paresthesias in the previously treated area that gradually became a deep aching pain. Nine months after his initial treatment, he noted a droopy left upper lid followed by double vision and a firm left brow nodule.

An ophthalmologist found left ocular ductional deficits in addition to left upper lid ptosis and suspected a third cranial nerve palsy. Results of a nondedicated brain MRI were interpreted as normal.

Our examination disclosed 4 mm of left upper lid ptosis. Pupils measured 5 mm on the right, reacting briskly to direct light, and 7 mm and very irregular on the left without reaction to direct light. Adduction, supraduction, and infraduction were partially reduced in the left eye. There was hypesthesia over the left V1. A firm nodule was palpated above the left superior orbital rim. All other aspects of the neuro-ophthalmologic examination were normal.

High-resolution brain MRI with trigeminal nerve protocol showed a lobular left forehead mass (Fig. 1A) and enlargement of the left supraorbital nerve (Fig. 1BC). A subtle enhancing soft tissue lesion was seen in the anterior aspect of the left cavernous sinus (Fig. 1D). The presumptive diagnosis was perineural spread of skin cancer along V1 into the cavernous sinus (Fig. 2AB).

Biopsy of the solid skin nodule showed invasive squamous cell carcinoma. Local radiation performed elsewhere did not arrest the disease process. Within months, the patients had developed several more scalp nodules and proptosis. He died 20 months after the treatment of his skin tumor and 8 months after diagnosis of perineural spread.

Case 2
A 65-year-old woman experienced paresthesias in her left cheek. One month later she noted reduced vision in the left eye that gradually worsened. Left proptosis soon followed. Brain and orbit MRI was interpreted as showing a mass in the left posterior orbit (Fig. 3A). Local meningioma and lymphoma were in the differential diagnosis.

Our examination 3 weeks later showed a best-corrected visual acuity of 20/15 in the right eye and 20/40 in the left eye, a left afferent pupillary defect, and mild left
proptosis. A nerve fiber bundle defect was present in the visual field of the left eye. Ophthalmoscopy showed slight temporal optic disc pallor in the left eye. All other aspects of the neuro-ophthalmological examination were normal, including examination of trigeminal function.

Review of the outside MRI confirmed the presence of the posterior orbital mass (Fig. 3A) but also disclosed a mass in the left hard palate (Fig. 3B) with perineural spread via the greater and lesser palatine nerves into the left pterygopalatine fossa (PPF) (Fig. 3C) and anteriorly into the left orbital apex via the left V2 and Vidian nerves (Fig. 3D). The presumptive diagnosis was a left palatal carcinoma with perineural spread along the greater and lesser palatine nerves into the PPF and then along V2 into the left orbit (Fig. 4A).

Biopsy of the hard palate mass disclosed a large B-cell lymphoma. Results of systemic staging were negative. She was treated with corticosteroids and chemotherapy. Within 6 months, visual symptoms and paresthesias had resolved, but we have not undertaken a follow-up examination.

**Case 3**

A 60-year-old man was noted to have 2 lesions on the left ear, one extending into the external auditory canal. Biopsy disclosed squamous cell carcinoma. Three weeks later he developed a left seventh cranial nerve palsy thought to be due to tumor invasion. MRI showed abnormal soft tissue thickening and enhancement involving the left periauricular region, the extracranial portion of the left seventh cranial nerve, and the area posterior to the mandibular condylar neck (Fig. 5AB) with suspected involvement of the left auriculotemporal (AT) nerve, a branch of the V3.

The patient underwent total parotidectomy and auriculectomy with facial nerve sacrifice, selective neck dissection, and lateral temporal bone resection. Histopathologic examination demonstrated moderately differentiated squamous cell carcinoma with bony and perineural invasion.

Two months after completing local radiation and chemotherapy, the patient reported left-sided jaw pain like an “electrical sensation,” attributed to the surgery.
Case 1. Schematic illustration of Figure 1. A. Axial view shows that forehead squamous cell carcinoma has spread along the left supraorbital branch of V1 to the cavernous sinus. B. Coronal view shows that the tumor has extended from V1 (black arrow) to the third cranial nerve (arrowhead) and fourth cranial nerve (white arrow), probably via nervi nervorum.
However, a routine surveillance MRI 2 months later disclosed left middle ear cavity recurrence and a mass in the left Meckel’s cave (Fig. 6A) with enhancement along V3 (Fig. 6B).

He underwent another round of radiation and 6 cycles of chemotherapy. Despite these treatments, he developed extensive involvement of the cisternal segment of the left trigeminal nerve (Fig. 7A) and antegrade involvement of the left inferior alveolar nerve (Fig. 7B). He died 23 months after the initial diagnosis. The presumptive diagnosis was perineural spread along the AT nerve with spread to Meckel’s cave and then to other branches of V3 and the trigeminal root (Fig. 8A–B).

**DISCUSSION**

We have presented the clinical and imaging findings of single cases demonstrating perineural spread of squamous cell carcinoma along V1, V2, and V3. The V1 case was initially believed to be a compressive third cranial nerve palsy. The V2 case was initially diagnosed as a primary intraorbital mass. The V3 case was considered to be a squamous cell carcinoma limited to the region of the left ear.

Overlooking perineural spread of head and neck cancer occurs because of incomplete understanding of the clinical manifestations, the anatomy of the sensory and motor nerves of the head and neck, and the often subtle imaging signs. Although some studies have estimated that up to 30%–45% of patients may be asymptomatic even with extensive perineural spread (5), more often the clinical manifestations are subtle and overlooked by the physician. The most common initial symptoms of trigeminal perineural spread are painful dysesthesias and numbness. Hypesthesia is often found on examination (6). Trigeminal motor weakness (of masticator, pterygoid, or temporalis muscles) is usually a much later finding (6,7).

Familiarity with the innervation of the head and neck will allow the clinician to predict likely areas of perineural spread based on the location of the tumor. V1 innervates the forehead, orbit, eye, frontal sinus, lacrimal gland, and dorsum of the nose (8). Tumors in these areas of the face tend to spread along this division. Tumors of the mid-face tend to spread along V2, which serves the skin over the zygomatic arch, anterior temporal region, cheek, lower lid, lateral portion of the nose, upper lip, and maxillary sinus (3,8). V3 carries tumors located in the anterior portion of the ear, and the skin and mucosa of the lower portion of the
FIG. 4. Case 2. Schematic illustration of Figure 3. Coronal (A) and sagittal (B) views show lymphoma originating in the left palate (arrow) which has spread from the hard palate via greater and lesser palatine nerves to the pterygopalatine ganglion (B, arrowhead) and then via a V2 branch into the orbit.
FIG. 5. Case 3. Perineural spread of squamous carcinoma along the third trigeminal division (V3): initial scan. Precontrast T1 axial (A) and T2 axial (B) MRI images display a hypointense right parotid mass (arrows) posterior to the mandibular ramus and along the expected course of the auriculotemporal nerve. Lateral and anterior extension was suspicious for facial nerve involvement as well.

FIG. 6. Case 3. Perineural spread of squamous cell carcinoma along the third trigeminal division (V3): 6 months later. A. Postcontrast T1 axial MRI shows an enhancing mass in the left Meckel’s cave (arrows). B. Postcontrast T1 coronal MRI shows enhancement and enlargement of the left V3 (arrows).

FIG. 7. Case 3. Perineural spread of squamous cell carcinoma along the third trigeminal division (V3): 12 months later. A. Postcontrast T1 axial MRI shows retrograde extension of tumor along the cisternal segment of the left trigeminal nerve (arrow). B. There is antegrade extension of tumor into the left inferior alveolar nerve that enhances (arrows). Compare with the normal unenhancing inferior alveolar nerve in the right mandibular foramen (arrowhead).
FIG. 8. Case 3. Schematic illustration of perineural spread of squamous cell carcinoma along the third trigeminal division (V3). Sagittal (A) and coronal (B) views show tumor spreading from the parotid gland along the auriculotemporal branch of V3 to the trigeminal ganglion (A) via the foramen ovale (B).
cheek, chin, and lower lip. Tumors of the parotid gland travel along the facial nerve or AT branch of V3 (7–9).

With high field strength magnets, thin sections, and fat suppression, the changes associated with perineural spread should be evident to careful readers in 95% of patients (10). MRI changes include 1) alterations in the normal fat planes surrounding the nerve or within the basal skull foramina, 2) subtle enhancement of the involved nerve, and 3) enlargement of the involved nerve. CT changes include bone erosion and enlargement of the basal skull foramina (7). On MRI or CT, cavernous sinus involvement is evident as a convex bulge of its lateral wall (11).

Collaboration between the clinician and the radiologist plays a critical role in detection of perineural spread. Detailed requisitions including signs and symptoms help the radiologist assign the correct protocol for the study and focus on critical areas that may otherwise be overlooked. However, the entire course of the nerve must be evaluated, given the noncontiguous nature of the spread.

Recognizing perineural involvement has important implications for treatment and prognosis. Once perineural spread has been recognized, treatment will usually take the form of radiation or chemotherapy rather than surgery. If surgery is to be performed, it must encompass a much wider region (4). In some cases, a multifocal hematopoietic tumor may be the cause (as in our Case 2), in which case aggressive chemotherapy may be curative.

REFERENCES
Abstract: A 27-year-old man developed a persistent bitemporal hemianopia after severe head trauma sustained in a high-speed motor vehicle accident. The initial brain MRI revealed hemorrhagic contusion of the optic chiasm. A brain MRI performed 4 weeks later demonstrated complete chiasmal transection, a phenomenon rarely documented with imaging.

A 27-year-old male pedestrian was hit by a car while he was crossing the highway. The initial Glasgow Coma Scale score was 8 with reactive pupils bilaterally. Non-contrast brain CT revealed multiple bilateral orbital wall and facial fractures including the sphenoid walls, but there was no evidence of muscle entrapment or optic nerve sheath pathologic changes.

Full ophthalmologic examination performed 5 days after the trauma disclosed a visual acuity of 20/50 in both eyes. Pupils measured 4.5 mm in the right eye and 2.5 mm...
in the left eye without relative afferent pupillary defect. Visual fields by confrontation revealed a complete bitemporal hemianopia, which was later confirmed by Goldmann perimetry (Fig. 1A). There was substantially reduced infraduction of the right eye and abduction of the left eye, resulting in binocular diplopia. The right upper lid was ptotic. Results of slit-lamp examination and ophthalmoscopy were unremarkable.

Orbit MRI revealed an enlarged and distorted optic chiasm with normal optic tracts and optic nerve sheath complexes (Fig. 1B). These MRI findings were most consistent with intrinsic hemorrhage and edema of the chiasm. Given that this finding would predispose to a compartment syndrome, a trial of high-dose corticosteroids was initiated. However, the trial was discontinued the following day because of evidence of a cerebrospinal fluid (CSF) fistula and the possibility of returning to the operating room for fistula repair. Four weeks later, brain MRI showed complete longitudinal transection of the optic chiasm (Fig. 1C).

Follow-up examination 8 weeks after the accident revealed visual acuities of 20/30 in the right eye and 20/60 in the left eye and no improvement in visual fields. Abduction was still reduced in the left eye. Discs showed mild pallor. Over the following 9 months, examinations disclosed no further changes.

Ever since the first description of traumatic chiasmal disruption by Nieden in 1883 (1), there have been only a few reports (2–9). One study of 90 patients sustaining injuries to the visual pathway (2) revealed traumatic chiasmal injury in only 4.4%. Among the reported cases (2–9), only a handful of patients have shown complete transection of the optic chiasm on imaging (4,5,8,9).

Traumatic injury to the optic chiasm occurs most frequently when the impact is in the frontal area, usually resulting in severe frontal head trauma accompanied by multiple cranial fractures (3,4,6,9,10). Survivors usually have sustained trauma to the cranial nerves, hypothalamus, and internal carotid artery (11). In one study, 68% had skull fractures (21% frontal, 16% basal, and 31% frontal and basal). The others (32%) had closed head injuries, and the majority of these had subarachnoid and intracerebral hemorrhages (11). Other findings have included cranial nerve deficits (anosmia, blindness, ocular motility defects, and deafness), diabetes insipidus, CSF rhinorrhea, carotid-cavernous fistula, carotid aneurysm, meningitis, panhypopituitarism, intrasellar hematoma, and pneumatocele (5,6,9). Gurses et al. (10) reported a young man who presented 4 months after severe head trauma with polyuria, polydipsia, anosmia, and constricted visual fields due to traumatic chiasmal syndrome (Fig. 2).

Figure 3 provides a gross and histopathologic view of a tear in the chiasm (12). The three proposed mechanisms of such an injury include direct tearing, external compression, and ischemic necrosis.

Direct shear injury of the optic chiasm is most often seen in severe central blows to the face (4). This proposed mechanism was initially rejected based on a study done on cadaver models, which showed that the intracranial distance between the optic foramina needs to be stretched from 12 to 22 mm for the chiasm to be transected (13). Such a degree of stretching was assumed to be an unlikely scenario for survivors of basilar skull fractures (5). However, using MRI, which allows clear visualization of the transected...
chiasm, it is understood that damage in vivo can range from micro-tears deep within the chiasm to complete sagittal bisection in response to severe frontal impact (11). Such a direct mechanism of injury results in a permanent axonal injury at the moment of impact, and the visual deficit is instantaneous and irreversible (11).

In contrast, indirect mechanisms can cause progressive damage to the optic nerve axons to develop hours after the injury. The optic chiasm can be compressed either by a downward herniation of the gyrus rectus (14) or via compression from hemorrhages surrounding the optic chiasm (15). This process may occur without severe axonal injury, explaining the visual field recovery observed in a few cases (13) and suggesting the need for early and appropriate decompression.

Contusion necrosis, cited as the most common mechanism of chiasmal injury after head trauma (16), damages axonal neurons by secondary axotomy. Damage to the microcirculation of the intracanalicular optic nerve axons results in compressive edema (11). This process causes further compression of axons within the fixed diameter of the bony optic canal, precipitating a positive feedback loop aggravated by an intracanalicular compartment syndrome (17,18).

Because chiasmal trauma is rare, guidelines for its management do not exist. Many studies have investigated the use of high-dose intravenous corticosteroids and optic canal decompression (19). However, results are conflicting and inconclusive. Therefore, most physicians make treatment decisions empirically. In one series of 19 patients by Hassan et al (11), 15 (75%) were left with a visual acuity of 20/40 or better in at least one eye, as was the case in our patient. However, 10 (50%) remained with no light perception in one eye.

REFERENCES
Intracranial Displacement of the Eye After Blunt Trauma

Zinat Miabi, MD, Nariman Nezami, MD, Mehran Midia, MD, and Ramin Midia, MD

Abstract: A 67-year-old man fell accidentally from a tractor. His right eye struck a protruding part of the vehicle. He experienced massive bleeding from his right eye and a 3 to 5-minute period of unconsciousness. Eight hours later, he was brought to the emergency unit of an ophthalmology hospital where examiners could not find the right eye and believed it to have been completely destroyed. However, CT disclosed that the eye, apparently still intact, had been displaced into the anterior cranial fossa through a fracture in the orbital roof. This is the first documentation of such a phenomenon.

A 67-year-old man fell from an agricultural vehicle and struck his right eye on a protruding element. Eight hours later, he was brought to the emergency unit of an ophthalmology hospital where examiners could not find the right eye and believed it to have been completely destroyed. However, CT disclosed that the eye, apparently still intact, had been displaced into the anterior cranial fossa through a fracture in the orbital roof. This is the first documentation of such a phenomenon.

FIG. 1. A. Coronal CT shows the apparently intact right eye dislocated superomedially through a large right orbital roof defect. B. Sagittal CT shows that at least half of the eye is situated in the anterior cranial fossa. There is an associated anterior frontal lobe contusion. C. Axial CT shows that the herniation is partially through the ethmoid sinus.
The Fisher Variant of Guillain-Barré Syndrome (Fisher Syndrome)

Lee A. Snyder, MD, Vivian Rismondo, MD, and Neil R. Miller, MD

Abstract: Fisher syndrome (FS) is an acute polyneuropathy typically characterized by the triad of ataxia, areflexia, and ophthalmoplegia, although it may present with 2 or even just 1 of these clinical findings. Similarities between FS and other acute polyneuropathies such as Guillain-Barré syndrome (GBS) and Bickerstaff brainstem encephalitis (BBE) suggest that FS is part of a spectrum of autoimmune disorders that may affect the peripheral and/or central nervous system. Anti-GQ1b antibody is present in the serum of more than 85% of patients with FS, but it is not specific to FS. Why some patients develop FS and others develop typical GBS or one of its other variants is still largely unknown.


The clinical triad of ataxia, areflexia, and ophthalmoplegia was first described by Collier in 1932 as a variant of the Guillain-Barré syndrome (GBS) (1). In 1956, Charles Miller Fisher reported 3 patients with this disorder, postulated that it represented a distinct clinical variant of GBS with a good prognosis (2), and pointed out that more invasive techniques such as cerebral angiography, previously used in evaluating such patients, were not necessary (3). The disorder became known as the Miller Fisher syndrome or simply “Fisher’s syndrome” in 1957, when Smith and Walsh (4) used the term in describing 2 additional patients with facial weakness and paresthesias. (Because Miller is Fisher’s middle name, we will follow their lead in this review and refer to the condition as Fisher syndrome [FS]).

Although most published reviews define FS strictly as an acute monophasic illness featuring the clinical triad of ophthalmoplegia, ataxia, and areflexia, it can present with 2 or even 1 of these features. It can also present with features that overlap Bickerstaff brainstem encephalitis (BBE), a syndrome characterized by ophthalmoplegia, ataxia, impaired consciousness, and hyperreflexia (5), and with features typical of GBS, in which limb weakness is the most prominent finding, sometimes accompanied by sensory loss and nonocular motor cranial neuropathies (6). These disorders can all develop after an antecedent infection and share a characteristic elevation of cerebrospinal fluid (CSF) protein.

The identification of the GQ1b autoantibody, present in most patients with FS, has further transformed thinking about the nosologic position of this syndrome. FS is now widely regarded as belonging to a spectrum of acute inflammatory polyneuropathies that includes BBE, anti-GQ1b-positive acute ophthalmoparesis without ataxia (AO), ataxic GBS, and GBS with ophthalmoplegia (7,8) (Table 1). The ability to test for the presence of the anti-GQ1b antibody has made the diagnosis of FS more consistent and has allowed for a greater appreciation of FS-related disorders.

The marked variability in the clinical presentation of FS has blurred the lines between FS in its purest form and related clinical syndromes that defy classification (Table 2). In this article we review the demographics as well as the neuro-ophthalmic and systemic symptoms and signs, ancillary tests, natural history, and treatment options for disorders that can together be grouped as the Fisher variant of GBS.

INCIDENCE AND DEMOGRAPHICS

The worldwide incidence of GBS is 1–2 per 100,000 per year (9), with FS as a percentage of such cases varying depending on geography. Whereas FS has been reported at a rate of 1%–7% of GBS in countries in the Western hemisphere (10–15), it is much more common in Asia, comprising 18%–19% of cases of GBS studied in Taiwan (16,17) and 25% of GBS in Japan (18). Men are somewhat more often affected than women, making up 60% and 68% of those with FS in 2 large series (18,19). Male predominance is also found in related disorders such as AO.
and BBE (19–21). FS has been described in people of all ages, including infants (22), although it is less common in children than in adults (23). A retrospective study of 466 patients with FS reported a median age of onset of 44 years with a bimodal age distribution peaking between 30 and 39 years and 50 and 59 years (19). There is dispute about a seasonal predilection for FS, with studies showing a rise in new cases in the spring (20,24–27), winter (17), summer, and fall (20).

ANTECEDENT INFECTIONS

The variability in seasonal occurrence of FS may be related to the typically postinfectious nature of this disorder. Prodromal upper respiratory symptoms are experienced more commonly than gastrointestinal symptoms (18,28). The median time from onset of prodromal to neurologic manifestations was 8 days in 1 large series (18).

Campylobacter jejuni is the most commonly identified agent causing antecedent infection in patients with acute FS and those with GBS and related disorders, followed by Haemophilus influenzae. However, in most patients, no definite infectious association has been detected (29). In 1 large study, 21% of patients with FS had positive titers for C. jejuni, 8% for H. influenzae, 4% for cytomegalovirus, and 3% for Mycoplasma pneumoniae (19). Less common antecedent infectious agents associated with FS are Epstein-Barr virus (30), group A streptococcus (31), Coxiella burnetii (32), Pasteurella multocida (33), Helicobacter pylori (34), Aspergillus species (35), and varicella zoster (36). FS also has been reported after inoculation with the influenza vaccine (37) and after vaccination with Pneumovax (38). An association does not allow a causal relationship to be inferred (39,40).

A common infectious etiology links FS with related disorders. In one study of 21 patients with AO, 81% experienced symptoms of antecedent infection, with 57% having symptoms of an upper respiratory tract infection (41). C. jejuni was isolated from 1 of those patients (41). In another series, 96% of 53 patients with BBE reported prior infectious symptoms, again mostly respiratory (19). Kimoto et al (42) reported on the spectrum of neurologic disorders that occurs subsequent to C. jejuni enteritis, including, in descending order of frequency, GBS, FS, muscle stretch reflex-preserved GBS, FS/GBS overlap, acute oropharyngeal palsy, BBE, BBE/GBS overlap, AO, and ataxic GBS. They correlated these groups with genotypic variations and proposed that the conditions were on a continuum.

CLINICAL ASSOCIATIONS

FS occasionally develops spontaneously in patients with various autoimmune, neoplastic, or infectious diseases such as myasthenia gravis (43–45), systemic lupus erythematosus (46,47), Still disease (48), thyroid disease (49,50), Hodgkin disease (51), lung cancer (52), leptomeningeal signet-ring cell carcinomatosis (53), Burkitt lymphoma (54), chronic lymphocytic leukemia (55), and AIDS (56). It has also been reported in patients after treatment with several medications, including tacrolimus (57), the antiretroviral agent stavudine (24,58), and tumor necrosis factor antagonists (59,60). These associations may be fortuitous.

CLINICAL FEATURES

In its purest form, FS is a triad of acute ophthalmoplegia, ataxia, and areflexia, although even the initial descriptions of the condition include patients with

<table>
<thead>
<tr>
<th>Clinical syndromes associated with the anti-GQ1b antibody</th>
<th>Fisher Syndrome</th>
<th>Acute Ophthalmoparesis</th>
<th>Bickerstaff Brainstem Encephalitis</th>
<th>Guillain-Barré Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical characteristics</td>
<td>Ophthalmoplegia, ataxia, hyporeflexia or areflexia (2)</td>
<td>Ophthalmoplegia (41, 68)</td>
<td>Ophthalmoplegia, ataxia, impaired consciousness, hyperreflexia (5)</td>
<td>Weakness, sensory loss, cranial neuropathy, areflexia (89)</td>
</tr>
<tr>
<td>Rate of anti-GQ1b positivity</td>
<td>Up to 95% (24, 67)</td>
<td>Unknown (100% is required for diagnosis of “anti-GQ1b-positive acute ophthalmoparesis without ataxia”)</td>
<td>Up to 68% (19)</td>
<td>Up to 83% in patients with ophthalmoplegia (67); more strongly correlated with other anti-ganglioside antibodies (196)</td>
</tr>
</tbody>
</table>

Other clinical features common to the syndromes listed above include antecedent infection within the last 4 weeks and CSF albuminocytologic dissociation (8).
### TABLE 2. Clinical findings in Fisher syndrome and related disorders

<table>
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<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>466</td>
<td>62</td>
<td>50</td>
<td>32</td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>60%</td>
<td>45%</td>
<td>68%</td>
<td>—</td>
</tr>
<tr>
<td>Female</td>
<td>40%</td>
<td>55%</td>
<td>32%</td>
<td>—</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>44</td>
<td>42</td>
<td>40</td>
<td>45 (mean)</td>
</tr>
<tr>
<td>Antecedent illness</td>
<td>90%</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Respiratory symptoms</td>
<td>76%</td>
<td>67%</td>
<td>76%</td>
<td>56%</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>25%</td>
<td>26%</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Respiratory and gastrointestinal symptoms</td>
<td>12%</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Serologic testing†</td>
<td>73 patients tested</td>
<td>44 patients tested</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Campylobacter jejuni</td>
<td>21%</td>
<td>18%</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Haemophilus influenzae</td>
<td>8%</td>
<td>2%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>4%</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Mycobacterium pneumoniae</td>
<td>3%</td>
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<tr>
<td>Initial symptom</td>
<td></td>
<td></td>
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<tr>
<td>Diplopia</td>
<td>65%</td>
<td>38%</td>
<td>78%</td>
<td>—</td>
</tr>
<tr>
<td>Gait disturbance</td>
<td>32%</td>
<td>24%</td>
<td>46%</td>
<td>28%</td>
</tr>
<tr>
<td>Diplopia and ataxia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysesthesias</td>
<td>14%</td>
<td>21%</td>
<td>14%</td>
<td>16%</td>
</tr>
<tr>
<td>Consciousness disturbance</td>
<td>0%</td>
<td>0%</td>
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<td>—</td>
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<tr>
<td>Blepharoptosis</td>
<td>4%</td>
<td>2%</td>
<td>2%</td>
<td>9%</td>
</tr>
<tr>
<td>Limb weakness</td>
<td>2%</td>
<td>2%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Bulbar dysfunction</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>19%</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>—</td>
<td>—</td>
<td>—</td>
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</tr>
<tr>
<td>Photophobia</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Dizziness</td>
<td>—</td>
<td>—</td>
<td>2%</td>
<td>—</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>28%</td>
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<tr>
<td>Headache</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>34%</td>
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<tr>
<td>Facial weakness</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>13%</td>
</tr>
<tr>
<td>Neurologic signs during illness</td>
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<tr>
<td>External ophthalmoplegia</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
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<tr>
<td>Complete</td>
<td>—</td>
<td>—</td>
<td>30%</td>
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<td>Binocular</td>
<td>—</td>
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<td>Horizontal and vertical</td>
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<td>Horizontal only</td>
<td>—</td>
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TABLE 2. Continued

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<tbody>
<tr>
<td></td>
<td>FS</td>
<td>*Unclassified</td>
<td>FS</td>
<td>AO</td>
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<td>Vertical only</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Pupillary dysfunction</td>
<td>35%</td>
<td>32%</td>
<td>42%</td>
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<td>Ataxia</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
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<tr>
<td>Deep tendon reflexes absent or decreased</td>
<td>100%</td>
<td>0%</td>
<td>100%</td>
<td>100%</td>
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<tr>
<td>Deep tendon reflexes normal or brisk</td>
<td>0%</td>
<td>100%</td>
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<tr>
<td>Limb weakness</td>
<td>25%</td>
<td>24%</td>
<td>20%</td>
<td>25%</td>
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<tr>
<td>Blepharoptosis</td>
<td>37%</td>
<td>32%</td>
<td>58%</td>
<td>59%</td>
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<tr>
<td>Facial weakness</td>
<td>22%</td>
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<td>32%</td>
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<td>Bulbar palsy</td>
<td>17%</td>
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<td>26%</td>
<td>59%</td>
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<td>Babinski sign</td>
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<td>Trigeminal dysfunction</td>
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<td>—</td>
<td>16%</td>
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<td>Sensory disturbance</td>
<td>52%</td>
<td>42%</td>
<td>—</td>
<td>59%</td>
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<td>Dysesthesia</td>
<td>45%</td>
<td>40%</td>
<td>24%</td>
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<tr>
<td>Superficial sense impairment</td>
<td>7%</td>
<td>8%</td>
<td>20%</td>
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<tr>
<td>Deep sense impairment</td>
<td>17%</td>
<td>13%</td>
<td>18%</td>
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<tr>
<td>Sinus tachycardia</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>3%</td>
</tr>
<tr>
<td>Micturition disturbance</td>
<td>—</td>
<td>—</td>
<td>16%</td>
<td>3%</td>
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<tr>
<td>Laboratory tests</td>
<td>—</td>
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<tr>
<td>Cerebrospinal fluid cytoalbuminous dissociation‡</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>14%</td>
</tr>
<tr>
<td>Within 1 week</td>
<td>37%</td>
<td>30%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Within 2 weeks</td>
<td>76%</td>
<td>54%</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Anti-GQ1b-positive</td>
<td>83%</td>
<td>58%</td>
<td>89% of 36 patients tested</td>
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</tr>
<tr>
<td>Anti-GT1a-positive</td>
<td>78%</td>
<td>66%</td>
<td>—</td>
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<tr>
<td>Neuroimaging§</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
<td>MRI Abnormality</td>
<td>1%</td>
<td>7%</td>
<td>—</td>
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<tr>
<td>Outcomes</td>
<td>Median time to nadir (days)</td>
<td>4%</td>
<td>—</td>
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<td></td>
<td>Assisted ventilation</td>
<td>1%</td>
<td>0</td>
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</table>

*Unclassified patients exhibited ophthalmoplegia and ataxia but not areflexia.
—, data not reported.
†A subgroup of patients underwent serologic testing.
‡The majority of patients in the Ito et al study underwent CSF testing.
§The majority of patients in the Ito et al study underwent MRI testing.
FS, Fisher syndrome; AO, acute ophthalmoplegia without ataxia.
additional findings such as mild limb weakness or drowsiness (2).

**Symptoms**

The initial symptom in FS is typically diplopia (65%), followed by gait disturbance (32%) (19). These symptoms were described as occurring simultaneously in 14% of patients with FS (19). Dysesthesias are also commonly reported, occurring in 14% of patients with FS in 2 large studies (18,19). Less common presenting symptoms are blepharoptosis, mild limb weakness (19), dysphagia, photophobia (18), blurred vision, dizziness, headache, and facial weakness (16). One man with FS and positive serum anti-GQ1b autoantibodies presented with a severe and persistent headache that the authors postulated was due to antibody-mediated effects on the trigeminovascular pain pathway (61).

**Ophthalmoplegia**

Ophthalmoplegia seems to be the most prevalent and consistent finding in FS and related disorders during the acute phase of the illness (19) and can manifest as various combinations of deficits (21) (Fig. 1). Ophthalmoplegia is closely tied to the presence of anti-GQ1b antibodies, although these antibodies also can be found in patients with no eye movement abnormalities (8,62). Most patients with FS exhibit bilateral, relatively symmetrical ophthalmoplegia, but the condition also can be unilateral (41,63–65). Up to one third of patients have complete external ophthalmoplegia (18). A review of 31 patients with complete bilateral ophthalmoplegia during a 34-year period (66) revealed that FS was the most common cause and, together with GBS, was responsible for 58% of such cases.

The ophthalmoplegia seen in FS is similar to that described in AO (21). A study that compared the findings in 11 anti-GQ1b antibody-positive patients with AO to the findings in 20 anti-GQ1b antibody-positive patients with other disorders including FS concluded that the patterns of ophthalmoplegia were similar in these groups. Abduction deficit was the most common finding, occurring in 73% (21). The association of acute ophthalmoparesis with the anti-GQ1b antibody was identified in 1993, when Chiba et al (67) described 5 patients with isolated ophthalmoparesis, 4 of whom had had a common cold as a prodrome, the fifth having had diarrhea. All had evidence of mild bilateral sixth cranial nerve palsy, and the condition was designated “atypical FS.” Interestingly, 2 patients in that study who were negative for anti-GQ1b antibody (1 with typical FS and 1 with GBS with ophthalmoplegia) had isolated complete unilateral sixth cranial nerve palsy, suggesting that

**FIG. 1.** Bilateral mydriasis, pupillary areflexia, and impaired supraduction in Fisher syndrome. A 17-year-old college student developed photophobia, diplopia, and paresthesias 1 month after a febrile illness. Blood tests were positive for IgG and IgM antibodies against Epstein-Barr viral antigens and showed elevated levels of GQ1b autoantibodies. Her pupils did not constrict to direct light or a near target.
a different mechanism and pattern of ophthalmoplegia might be present in anti-GQ1b antibody-negative patients (67).

Yuki et al (68) described 8 anti-GQ1b antibody-positive patients with ophthalmoplegia and no ataxia and termed the condition simply “acute ophthalmoparesis.” Two had horizontal and vertical gaze palsies; the other 6 had bilateral sixth cranial nerve palsies. Yuki et al (41) subsequently summarized the findings in 21 other patients with AO, most of whom had bilateral, horizontal, mostly abduction deficits. In this group, gaze deficits were bilateral in 76%. Both horizontal and vertical movements were affected in 48%, and 52% had gaze deficits limited to the horizontal plane. Bilateral abduction deficit was the most common pattern, occurring in 33% of patients. Other case series have confirmed that the most characteristic pattern of AO is an initial bilateral sixth cranial nerve palsy followed by third cranial nerve palsy with internal ophthalmoplegia (8,69), a pattern present in 48% of the 21 patients reported by Yuki et al (41). No studies have determined definitively the frequency of the anti-GQ1b antibody in patients with isolated ophthalmoplegia. However, in a study of 100 patients with isolated sixth cranial nerve palsies, when traditional etiologies such as diabetes mellitus, vascular disorders, trauma, or tumor were excluded, the anti-GQ1b antibody was present in the sera of 25%, indicating that some cases may be related to FS (70).

“Brainstem” Ocular Motor Deficits

Clinical findings suggestive of brainstem ocular motor deficits have been described in some patients with otherwise typical FS, suggesting the possibility of central nervous system (CNS) involvement (71,72). In a study of 50 patients with typical FS (18), 2 exhibited preservation of the Bell phenomenon despite paralysis of voluntary upgaze; 2 had gaze-evoked, horizontal, dissociated nystagmus; 1 showed preservation of convergence despite abduction palsy; and 1 had an internuclear ophthalmoplegia. Other forms of apparently CNS ocular motor dysfunction reported in patients with otherwise typical FS include dorsal midbrain syndrome with eyelid retraction (2), convergence spasm, divergence paralysis (73,74), saccadic dysmetria (75), defective vestibulo-ocular reflex despite recovery of upgaze, central vestibular nystagmus, and relative preservation of optokinetic nystagmus and preservation of the vestibulo-ocular reflex despite an otherwise complete ophthalmoplegia (76).

Internal Ophthalmoplegia

Internal ophthalmoplegia is quite common in FS and related syndromes, with the pupillary constriction to light and near stimulation ranging from slow to absent (21,77). Light-near dissociation may be present (78–80). All 3 patients initially reported by Fisher exhibited a sluggish pupillary constriction to light (2), and in the series of 50 patients with FS reported by Mori et al (18), mydriasis was present in 42%—about half of whom had anisocoria—and the pupillary constriction to light was sluggish in 42%. Of 11 patients with FS in a study linking FS to anti-GQ1b antibody positivity, 64% had absent or sluggish pupillary reflexes (81). Most of these findings were bilateral.

With regard to disorders that share the anti-GQ1b antibody, the incidence of internal ophthalmoplegia is highest in patients with FS exhibiting limb weakness (52%), followed by BBE (42%) and typical FS (37%) (8). Pupillary abnormalities seem to occur less commonly in patients with AO, as evidenced by the lack of pupillary defects in the study by Yuki et al (68) of 21 patients with AO and 7% involvement in the series of 15 patients reported by Odaka et al (8). Nevertheless, in 1 study of 11 patients with AO, about half had internal ophthalmoplegia (21). Patients with anti-GQ1b antibody positivity have also been reported to have internal ophthalmoplegia as the prominent feature with little or no external ophthalmoplegia (79,82,83). Many of these patients demonstrate denervation supersensitivity to cholinergic agents, suggesting ciliary ganglion or short ciliary nerve involvement (78,79).

Ataxia

Ataxia is often the initial presenting symptom in FS and can be quite severe, causing a gait disturbance so profound that, in 1 large series, 30% of affected persons could not walk independently (18). Ataxia in FS is associated with the anti-GQ1b antibody. This autoantibody also can be found in patients who have a variant of ataxia without ophthalmoplegia (84,85). One study showed that anti-GQ1b antibody-positive patients had more cerebellar-type severe ataxia than patients with FS who were antibody-negative (81). The autoantibodies seen in the ataxic forms of GBS also exhibit the same fine specificity patterns for other gangliosides as those seen in FS, further evidence that the 2 disorders are related (86).

The pathogenesis of the ataxia in FS is not completely understood. Both peripheral and central mechanisms have been implicated. Early studies showed a correlation between abnormalities in muscle fiber afferents and severity of ataxia, suggesting impaired proprioception as the mechanism (87,88). Indeed, postural sway analysis reveals selective dysfunction of proprioception in patients with FS (85,89) and BBE (19). Thus, dysfunction of muscle spindle afferent fibers may be responsible for the ataxia, at least in some patients (18,89,90). However, the presence of anti-cerebellar antibodies in the sera of patients with FS has led other investigators to suggest that the ataxia in such patients is cerebellar in origin (91,92). Additional research is needed to elucidate fully the pathophysiology of ataxia in FS and related syndromes.
**Areflexia**

Deep tendon areflexia is part of the classically described FS triad, although it is also part of typical GBS (6). The loss of reflexes was initially thought to be present in almost all patients with FS. However, reflexes are intact more often than originally believed (93). For example, in a series of 581 patients with FS and BBE who presented with acute ophthalmoplegia and ataxia, Ito et al (19) found that of the 528 patients with intact consciousness, 12% had normal or even accentuated deep tendon reflexes (19). In a review of 13 Korean patients with ophthalmoplegia and ataxia and anti-GQ1b antibody-positivity, 4 (31%) had normal reflexes (21). A 1992 review of the published reports of FS (23) concluded that 18.4% of patients had intact reflexes. Electrophysiologic studies support peripheral nerve dysfunction as the cause of reduced deep tendon reflexes (94,95).

**Other Manifestations**

Other findings often reported in patients with FS and related syndromes include various patterns of blepharoptosis, occurring in up to 58% of patients (18,23,41), and eyelid nystagmus (96). Dysesthesias can occur in 45% of patients during the acute phase of illness (19). Facial and bulbar palsies were described in 32% and 26%, respectively, in 1 large study (18). Limb weakness is a prominent and distinguishing feature of GBS as opposed to FS, but a mild decrease in muscle strength is commonly seen in FS (18). Several case reports have described bilateral and, less commonly, unilateral optic neuritis in FS (97–102). Headache is reported in FS and was present in 2 of Fisher’s original patients (2). Pain in FS can occur perioricularly and in the back and extremities (103,104). In a study by Koga et al (103), pain was described by 22% of 27 patients, half of whom localized the discomfort to the periorcular region, and was more common in children and young adults. Micturition disturbances were present in 16% of patients with FS in 1 large case series (18), and urinary retention also has been reported (17,105). Angle-closure glaucoma developed in a patient with FS in whom pupillary dysfunction occurred in the setting of a congenitally narrow anterior chamber angle (106). One patient with FS had unilateral absence of corneal sensation (107). Autonomic neuropathy can occur in FS but is less severe and less frequent than in GBS or BBE (105). In 1 study of cardiovascular autonomic function (108), subclinical autonomic dysfunction was identified in most patients with FS.

**LABORATORY FINDINGS**

**CSF Protein**

A rise in protein concentration in the cerebrospinal fluid (CSF) in 1 of Fisher’s original patients was the key piece of evidence that led the author to believe that the condition bore a close relationship to a “GBS type of polyneuropathy” (2). Elevation of CSF protein with minimal or no cellular reaction or “cytological dissociation,” may be absent at the time of initial symptoms, becoming prominent over the next weeks (109). It seems to occur more frequently in the overlap syndrome of BBE/GBS than in FS and occurs even less frequently in AO (8,41). However, it is difficult to compare CSF findings among these variants because the finding of elevated CSF protein depends on when in the course of the disease the specimen is collected, information that is not consistently reported.

**Anti-GQ1b Antibody**

The discovery of the frequent presence of the anti-GQ1b antibody in the acute-phase sera of patients with FS has helped clinicians understand the broader spectrum of FS and related disorders (7). This antibody was first reported in FS in 1992 by Chiba et al (7), who described 6 patients. This report and subsequent studies (109) have affirmed that this antibody, which cross-reacts with the GT1a ganglioside, is present in more than 85% of patients with FS. It is absent in normal control subjects and is found less often in patients with GBS without ophthalmoplegia (67,81,110,111). This autoantibody is also found in FS-related diseases such as GBS with ophthalmoplegia (67), AO (68), BBE (21,112), and ataxic GBS without ophthalmoplegia (86). Clinically, the presence of the anti-GQ1b antibody correlates with the presence of ophthalmoplegia (41) and ataxia (84) but has been reported in the absence of both (62). Odaka et al (8) described clinical similarities and variations among the diseases that constitute the “anti-GQ1b syndrome” and proposed this as further evidence that they are part of a clinically continuous range of illnesses.

The GQ1b ganglioside is a cell surface component that is concentrated in the paranodal regions of the human third, fourth, and sixth cranial nerves. It contains polysaccharides identical to the lipopolysaccharides (LPS) contained in the outer membranes of certain bacteria and may thus be the target of an immune response initiated against epitopes shared by these nerve fibers and various infectious agents (41). In 1994, Yuki et al (113) found that monoclonal antibodies to the GQ1b ganglioside reacted to LPS fractions from C. jejuni isolated from patients with FS. These investigators proposed that, through the mechanism of molecular mimicry, they were not only a marker for the disease, but actually played a role in its pathophysiology. Anti-GQ1b/GT1a antibodies also bind to LPS from FS-related H. influenzae strains, suggesting a common pathogenesis (29). The finding of these antibodies in the sera of patients with isolated internal ophthalmoplegia suggests that these epitopes may also be present in the ciliary ganglia (41,67,79,114).
Anti-GQ1b antibodies affect the neuromuscular junction, inducing axon and Schwann cell degeneration through complement-mediated pathways (115–119). Ganglioside complexes containing GQ1b have also been investigated as other possible targets for autoantibodies (120,121) whose specificity may be associated with the clinical features of GBS and FS (90). In addition, reactivity to minor gangliosides has been shown to be present in FS and related disorders and may prove to be helpful in their diagnosis and treatment (122).

In comparing the prevalence of CSF protein elevation with that of serum anti-GQ1b antibodies in the diagnosis of FS, Nishimoto et al (109) demonstrated that in the 1st week after onset of symptoms, anti-GQ1b antibodies were almost always present, whereas elevated CSF protein was found in only 25% of patients. They concluded that CSF findings are not as sensitive as the anti-GQ1b antibody assay in diagnosing FS in the early stage of the disorder. In addition, anti-GQ1b antibody titers have been shown to correlate with clinical severity of the disease, particularly ophthalmoplegia (123) and also demonstrate a relationship to disease course because they decline with clinical recovery (81,109).

NEUROIMAGING AND PATHOLOGIC STUDIES

Results of neuroimaging are usually unremarkable in patients with FS. However, in 1 large study (19), 1% of patients with FS had MRI abnormalities in the midbrain, cerebellum, or middle cerebellar peduncle. Other individual case reports have described MRI lesions in the brainstem (124–127); fourth (128), sixth (129), and seventh cranial nerves (130,131); spino-cerebellar tracts in the region of the lower medulla (132); lumbosacral roots (131); cauda equina (133); and posterior columns (134) of patients with FS. In general, lesions seen on MRI in patients with FS appear as hyperintense abnormalities on T2 images or, more commonly, as enhancing areas on postcontrast T1 images (127,130,135–138). Similar imaging abnormalities have been described in patients with GBS, although much less frequently (24).

A small number of necropsy studies have shown inflammatory brainstem lesions (23,139–141) as well as demyelination of peripheral nerves (142). In 1 patient with recurrent FS, demyelination and axonal impairment of the intra-axial portion of the third cranial nerve were present and associated with mild retrograde degeneration in the third, fifth, sixth, and seventh cranial nerve nuclei (143).

CLINICAL COURSE

Most patients with FS recover spontaneously and completely within 2–3 months of disease onset. In 1 study (18), the median time from onset of neurologic symptoms to beginning of recovery in 28 untreated patients was 12 days for ataxia and 15 days for ophthalmoplegia. The median time to full recovery was 1 month for ataxia and 3 months for ophthalmoplegia. At 6 months after illness onset, no patients had substantial disability. The recovery rate was unrelated to patient age, sex, evidence of prior infection, disability at illness peak, or latency to peak (18).

Although FS is typically regarded as a monophasic illness, recurrences have been reported (99,144–158). Patients may present differently during subsequent episodes (150). Chronic ophthalmoplegia associated with persistently high titers of anti-GQ1b antibody has been reported (159). Rarely, the disease can progress, and patients develop features similar to GBS, requiring more significant supportive care and mechanical ventilation (22,160–166). In a recent series, 1% of patients with FS required assisted ventilation compared with 34% of those with BBE (19). However, patients with FS who develop quadripareisis, often considered to have a “FS/GBS overlap,” are more likely to require mechanical ventilation than patients with typical GBS (167). Other serious complications in FS include coma (168), ballism (164,169), cardiomyopathy from dysautonomia (170), lactic acidosis (58), corticobulbar dysfunction (24,171), and life-threatening hypotension from inappropriate secretion of antidiuretic hormone (SIADH) (172). Death in FS is rare (142).

TREATMENT

Although no randomized, controlled clinical trials of treatment for FS have been performed (173), a retrospective analysis of 92 consecutive patients showed that treatment with intravenous immune globulin (IVIg) had no effect on overall outcome, presumably because patients with FS typically show good spontaneous recovery (174). Plasma- pheresis has also been used in selected patients with FS but without definite clinical benefit (175–185). As in all conditions in which spontaneous resolution is the rule, the risks of treatment in patients with FS must be balanced with the high likelihood of spontaneous recovery (186–190).

OVERVIEW

FS seems to represent a collection of manifestations derived from a spectrum of disorders that include GBS, BBE, and AO. The factors that determine which patients develop FS and which develop the related disorders remain unknown. The anti-GQ1b antibody is much more commonly associated with FS than with its related disorders, although patients with each of the disorders may have no serologic evidence of the antibody. When an infectious process caused by C. jejuni precedes the development of 1 of these conditions, the serotype of the responsible strain seems to influence the clinical presentation and the severity of the condition (29,191).
Host susceptibility probably also plays a role in phenotypic expression (192). Because the GQ1b antibody is found in sites unaffected by FS, its location in the body cannot be the only reason certain tissues are preferentially affected (114,115,193). For example, the antibody may have more access to certain structures through a compromised blood-brain barrier, perhaps leading to conditions more consistent with the CNS manifestations seen in BBE (85,89). Other factors may include the degree to which these gangliosides play a role in neural functioning or the “level of immunologic tolerance to microbial glycanics that mimic self gangliosides” (119).

Although the full immunologic cascade leading to FS has yet to be elucidated, the frequent finding of the GQ1b autoantibody is of great diagnostic value. Research into the molecular targets involved in the development of FS has already led to rational therapeutic studies in which monoclonal antibodies have shown success in treating murine models of the disorder (194,195). These investigations may ultimately clarify our understanding of the pathogenesis of FS and related disorders and lead to insights that will aid in treating more severe and generalized neuropahties.

REFERENCES


Complete Unilateral Ophthalmoplegia in Herpes Zoster Ophthalmicus

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Abstract: Based on a review of 20 well-documented cases reported in the English literature between 1968 and 2008, herpes zoster ophthalmicus (HZO) may rarely be associated with complete unilateral ophthalmoplegia, defined here as impaired ocular ductions in all 4 directions within 3 months of onset of manifestations of HZO. Ophthalmoplegia occurred equally in immune-competent and immune-incompetent individuals. HZO preceded ophthalmoplegia in 75% by a mean interval of 9.5 days and a range of 2 to 60 days, occurred simultaneously with ophthalmoplegia in 20%, and followed by 2 days the onset of ophthalmoplegia in only 5%. Concurrent conjunctival inflammation, keratitis, or anterior uveitis was present in 90%. Lumbar puncture showed features of aseptic meningitis in 88%, slightly more than the 40%–50% found in patients with HZO without ophthalmoplegia. On orbit/brain imaging, abnormal enlargement of the extraocular muscles was present in 33%, and orbital soft tissue swelling was present in 17%. Enhancement of ocular motor cranial nerves was not reported. Complete or near-complete resolution of ophthalmoplegia occurred in 65% within a range of 2 weeks to 1.5 years (mean 4.4 months). A single autopsy report described granulomatous angiitis of the meninges and large vessels in the anterior cerebral circulation, as well as periaxial infarction in the optic nerve, pons, and medulla but without viral inclusion bodies or antigen. Unsettled issues are whether the pathogenesis is direct viral invasion or an immune reaction to the virus, whether the impaired ocular ductions are based on myopathic or neuropathic injury, whether there are predisposing factors to the combination of HZO and complete ophthalmoplegia, and whether treatment is effective.

Herpes zoster ophthalmicus (HZO) refers to involvement of the ophthalmic division of the trigeminal nerve from reactivation of latent varicella zoster virus (VZV) harbored in the trigeminal sensory ganglion. It is characterized by an acute dermatomal eruption that evolves through papular, vesiculobullous, pustular, and crusting stages over days to 3 weeks. The zoster rash is often accompanied by periorcular pain and neurosensory disturbances in the first trigeminal division.

Ocular manifestations are observed in 20%–70% of patients with HZO, with involvement of every ocular structure (1). Postherpetic neuralgia is the most common neurologic sequela, but other neurologic complications, including cranial nerve palsies, stroke, myelitis, meningoencephalitis, and polyneuropathy, have also been reported (1,2).

Ocular motor cranial nerve palsies are reported in 5%–31% of patients, but the occurrence of complete unilateral ophthalmoplegia, defined here as concurrent unilateral impairment of ocular ductions in all directions, is rarer (2,3). In 1948, Edgerton (3) summarized 40 cases of unilateral ophthalmoplegia associated with HZO reported up to 1940. A review by Chang-Godinich et al (4) in 1997 included 16 cases reported from 1968 to 1997 and provided a comprehensive evaluation of this condition. However, that review did not include cases reported between 1948 and 1968 or 2 cases (5,6) reported much later with unusual clinical features. In addition, some of the reports included (7,9–11) contained very brief clinical information on the presentation, outcomes, and underlying systemic diseases, limiting a discussion on these aspects of this condition.

In this review the risk and prognostic factors, diagnostic utility of lumbar puncture and neuroimaging studies, efficacy of different treatment modalities, and the pathophysiologic basis of this condition in the light of recent neuroimaging findings will be addressed.
METHODS
A literature search was conducted on Medline, OVID, Cochrane Library, UpToDate, and Google Scholar databases using the key words: “herpes zoster ophthalmicus,” “complete ophthalmoplegia,” “external ocular nerve palsy,” “oculomotor,” “abducens,” and “trochlear” for articles published in the last 60 years (1948–September 2008). Articles published before these databases were established were gathered from references in the more recent articles. We defined complete unilateral ophthalmoplegia as impaired ductions in all 4 directions of gaze in the eye ipsilateral to the HZO occurring simultaneously or consecutively within 3 months of the onset of HZO.

We included only cases in which the abstracts and full articles were published in the English language. We excluded cases that had inadequate documentation of the underlying systemic conditions, clinical features, treatment, or clinical course. We excluded cases with bilateral ophthalmoplegia, with extraocular motility deficits in 3 or fewer directions of gaze, with involvement of 2 or fewer ocular motor cranial nerves, and without adequate documentation of HZO.

We adopted a hierarchical approach toward the selection of articles by applying the inclusion and exclusion criteria to the titles and abstracts of all articles and subsequently to the full reports. The articles were reviewed to determine the spectrum of clinical presentation, disease course, investigations, treatment modalities, and outcomes. Intraocular inflammation was present if there was evidence of corneal edema, keratitis, uveitis, vitritis, papillitis, or retinal necrosis. A successful clinical outcome was defined as complete or near-complete recovery of ophthalmoplegia with or without improvement in ptosis.

Based on the application of these inclusion criteria to the titles, abstracts, and full reports, we identified 17 articles comprising a total of 20 cases published between 1948 and September 2008 (4–6,12–25). Four articles comprising 8 cases, previously included in the analysis by Chang-Godinich et al (4) were excluded from this review based on at least 1 of the following reasons: 1) lack of clear documentation of underlying systemic conditions, clinical features, treatment, or outcome (7,9–11); 2) development of bilateral rather than unilateral ophthalmoplegia (10); and 3) absence of documented HZO (8). Eleven of the 17 included articles, representing 11 cases, were published between 1998 and 2008 (12–22).

CLINICAL FEATURES
Table 1 summarizes the clinical signs and symptoms, investigation findings, treatment, clinical course, and outcome for the 20 cases we reviewed.

There were 9 men and 11 women. The mean age was 66.2 ± 14.1 years with a range between 41 and 84 years. Nine patients (45%) were receiving medical immunosuppression, in the form of systemic corticosteroids or chemotherapy, or had underlying hematologic or solid organ malignancy or systemic connective tissue disease, including scleroderma or rheumatoid arthritis (4,12,14,20,23,24). Systemic treatment before the development of ophthalmoplegia included antiviral therapy (acyclovir or valacyclovir) alone in 7 patients (35%), corticosteroids alone in 1 patient (5%), and a combination of acyclovir and corticosteroids in 1 patient (5%) (4,6,13,15,17,18,20,22). Acyclovir was administered orally in 3 patients and intravenously in 4 patients; corticosteroids were administered orally in 1 patient and intravenously in 1 patient. Most patients (55%) had not received treatment before the onset of ophthalmoplegia.

HZO preceded the onset of ophthalmoplegia in 15 patients (75%) (4,6,13,15–18,20,22–25), with a mean time interval of 9.5 days (range 2–42 days), occurred simultaneously with ophthalmoplegia in 4 patients (20%) (5,12,14,21), and occurred 2 days after the onset of ophthalmoplegia in 1 patient (5%) (19) (Fig. 1). There was concurrent anterior segment involvement in 18 patients (90%) (4,6,12–25), including conjunctival inflammation, keratitis, and anterior uveitis. The severity of anterior uveitis was mild to moderate in all patients; none demonstrated a fibrinous reaction or hypopyon. Posterior segment abnormalities were observed in 4 patients (20%), including vitritis, blurring of the optic disc margins, and acute retinal necrosis (12,16,17,24,25).

The other presenting neuro-ophthalmic characteristics included complete or incomplete ptosis in all 20 patients (Fig. 2) (100%) (4–6,12–25), a fixed dilated pupil in 17 patients (85%) 4–6,12–14,16–17,20–25, optic neuropathy in the context of an orbital apex syndrome in 4 patients (20%) (4,12,23,24), and proptosis in 12 patients (60%) (4–6,12,15,18–20,23–25). An ipsilateral lower motor neuron facial nerve palsy was seen in 1 patient (5%) (21). Presenting clinical signs and symptoms suggestive of meningitis or encephalitis were seen in 5 patients (25%) (4–6,18,24).

Based on this review, complete unilateral ophthalmoplegia appears to be associated with HZO in older patients although it may occur in patients aged 50 years or younger. In the 3 patients younger than age 50, 1 had underlying scleroderma and previous treatment with penicillamine and plasmapheresis, which had been completed by an undocumented time interval before the presentation with HZO (6). The 2 remaining patients were not known to have any current or previous immune-compromising diseases or medical interventions (19,25).

Because the number of cases with complete unilateral ophthalmoplegia is small, meaningful conclusions on whether associated anterior and posterior segment,
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neuro-ophthalmic, or intracranial manifestations may be more frequent in this condition is difficult to establish. However, because adverse neurologic sequelae have been identified with this condition, a general recommendation can be made for an active neurologic assessment directed toward identifying signs of meningoencephalitis.

PREDISPOSING FACTORS

There is insufficient evidence to implicate any disease or treatment factors associated with the development of complete unilateral ophthalmoplegia in HZO.

The association between disseminated zoster and systemic corticosteroid therapy, hematologic malignancy, and HIV infection is well-recognized (26–29). In addition, progressive outer retinal necrosis (PORN) in HZO is strongly associated with HIV positivity (30). In contrast, there is no evidence that a reduction in immune status correlates with development of post-HZO neurologic sequelae such as stroke, meningoencephalitis, myelitis, or cranial neuropathy (31,32). In a recent study of neurologic complications in HZO, all patients were immunocompetent (33). In our review of complete ophthalmoplegia associated with HZO, there were 4 patients (20%) with lymphoproliferative disease or taking corticosteroids at the time of presentation. Because of the paucity of comparative evidence, it is difficult to conclude that an immunocompromised state predisposes to unilateral ophthalmoplegia.

A significant association between HZO-associated ophthalmoplegia and rash severity, iritis, and iris atrophy was reported by Marsh et al (11). However, this study did not account for possible confounding effects of each factor through multivariate analysis.

There is insufficient evidence to determine whether treatment of HZO with acyclovir or corticosteroid reduces the incidence of unilateral ophthalmoplegia. In this review, 40% of patients were managed with at least 1 type of antiviral agent (acyclovir or valacyclovir), and 10% were managed with systemic corticosteroids. In a recent case series of 4 patients who developed ophthalmoplegia after HZO (33), all had been treated with acyclovir before the development of this complication. The relatively low frequency of corticosteroid administration in 10% of patients probably reflects caution exercised in patients with known or suspected immune-compromising diseases or medical therapy. As with acyclovir, the efficacy of corticosteroid treatment in preventing unilateral ophthalmoplegia remains unsettled.

INVESTIGATIONS

In the 8 patients who had a lumbar puncture, the cerebrospinal fluid (CSF) profile was consistent with aseptic meningitis in 7 patients (88%) (4,6,13,14,18,19,24), comparatively higher than the 40%–50% found in HZO without ophthalmoplegia (34). Only 1 patient was tested for CSF varicella-zoster immune globulin, which
was elevated at 38.5 U/ml (18). However, CSF varicella zoster virus (VZV)-specific DNA analysis was not performed in the series reviewed. These CSF viral assays may be useful diagnostically in the small group of patients with HZO in whom ophthalmoplegia and meningeal symptoms present before the rash (19,35).

In the 9 patients who underwent CT and the 9 who underwent MRI intracranial and orbital imaging, the findings included abnormal enlargement of the oblique or rectus muscles (with and without tendon-sparing) in 6 patients (33%) (6,12,15,18,19,23), orbital soft tissue swelling in 3 patients (17%) (17–19), optic nerve enhancement in 2 patients (12%) (6,18), and meningeal and pontine trigeminal nucleus enhancement in 1 patient (6%) (6). Imaging also detected a pituitary adenoma in 1 patient (5), a cavernous sinus mass of uncertain diagnosis in 1 patient (20), and soft tissue swelling anterior to the globe in 1 patient (4). None of the scans showed ocular motor cranial nerve enhancement. Eight patients (44%) demonstrated normal imaging studies (4,13,14,16,21,22,24).

Visual evoked potentials, performed in 2 patients, showed reduced amplitude and delayed latency in 1 patient (18).

A single autopsy report (6) revealed granulomatous angiitis of the meninges, bilateral vasculitis of the large vessels in the anterior cerebral circulation, areas of subacute infarction in the pons and medulla, and periaxial infarction in the optic nerve. No viral inclusion bodies or antigens were detected.

**TREATMENT AND OUTCOME**

Therapy for HZO-associated ophthalmoplegia was initiated in 18 patients (90%), 3 patients having been treated with acyclovir alone (15%), 2 patients with systemic corticosteroids alone (10%), and 13 patients with...
a combination of acyclovir (or valacyclovir) and systemic corticosteroids (65%) (4–6,12–24). Agents were administered orally and intravenously.

At the end of the follow-up period, complete or near-complete resolution of ophthalmoplegia was observed in 13 patients (65%) (4,13,15–20,23,25), the time interval to resolution having a range of 2 weeks to 1.5 years and a mean of 4.4 months. Four patients (20%) were followed for periods of 5 weeks, 2 months, 8 months, and 3 years with minimal or no improvement in ophthalmoplegia or ptosis (12,14,21,22). The follow-up interval of 5 weeks and 2 months in 2 of these patients may have been too short to determine outcome. In the remaining 3 (15%) patients with ophthalmoplegia, its outcome could not be determined because of inadequate documentation in 1 patient (5) or other adverse events in 2 patients (6,24). One patient (24) developed Staphylococcus aureus endocarditis requiring evisceration of the eye. The second patient (6) who had scleroderma and developed ophthalmoplegia concurrent with meningoencephalitis 2 weeks after onset of HZO, at which time MRI demonstrated hyperintensities in the cerebral hemispheres and pons. The patient became comatose and died of sepsis. If these 3 patients are excluded from the analysis of outcome, the frequency of complete or near-complete resolution of ophthalmoplegia would be 76.5%.

Among the 13 patients who sustained near-complete or complete recovery of ophthalmoplegia, 11 also achieved full or near-complete recovery of ptosis, representing 55% of the 20 patients reviewed (4,13,15–20,23). There were no patients who achieved resolution of ptosis without concurrent resolution or improvement in ophthalmoplegia. Among the 17 patients described as having an ipsilateral fixed dilated pupil as an initial presenting sign, the outcome was described for only 8 patients (4,6,12,16,22–25), only 1 of which showed improvement in sphincter function (16). Resolution in optic neuropathy was seen in 3 of the 4 patients who manifested this sign at presentation (75%) (4,12,23,24). Postherpetic neuralgia was observed in 2 patients (10%) (4,15).

Based on this review, one cannot determine whether the clinical outcome was influenced by treatment. One cautionary note concerns the patient whose HZO was initially managed for up to 2 weeks with oral and topical steroids (6). Acyclovir was started only at the point when complete ophthalmoplegia and encephalopathy had developed, the only patient in the review in whom systemic steroids were initiated without systemic acyclovir cover. Orbital and intracranial MRI had demonstrated features of orbital pseudotumor syndrome and meningoencephalitis. The meningoencephalitis continued to progress over the next 2 weeks and eventually led to death of sepsis.

**PATHOPHYSIOLOGY**

The proposed mechanisms of ophthalmoplegia in HZO are a direct viral cytopathic effect and a reactive immunologic response to the virus (6,36). Support for a primary viral cause is suggested by the marked clinical response in 1 patient to an increased acyclovir dose and reduction of the prednisone dose (23). An immune mechanism would produce perineuritis, peripheral nerve demyelination, contiguous orbital inflammation, cranial vasculitis, myositis, brainstem encephalitis, and meningitis (4,6,12,15–19,36). Notably, granulomatous angiitis was the histopathologic lesion noted in the leptomeninges and carotid vessels in the patient with scleroderma described by Lexa et al (6). Although MRI findings support perineuritis as a pathophysiologic mechanism, none of the patients in this review demonstrated ocular motor nerve enhancement on neuroimaging. Instead, extraocular muscle enlargement (33%) and orbital soft tissue swelling (17%) were found on imaging. The high incidence of mydriasis (85%) and complete ptosis (70%) favors a neurogenic mechanism. HZO-associated ophthalmoplegia may thus involve multiple mechanisms.

**REFERENCES**

Reflections and Advice From an Aging Academic

Robert B. Daroff, MD


I appreciate the honor of being the Second Jacobson Lecturer and want to acknowledge my indebtedness to my two neuro-ophthalmologic mentors, Lawton Smith and Bill Hoyt. Bill is in the audience today and many of us were either trained by him or trained by someone who trained under him and certainly benefitted from his wisdom at these North American Neuro-Ophthalmology Society (NANOS) meetings.

When I was President of the American Neurological Association, I introduced Hoyt at the formal banquet by quoting President John F. Kennedy’s remarks to a group of Nobel laureates he had invited to the White House for lunch. Kennedy said, “Never in the history of the White House has there been such an accumulation of brain power, except perhaps when Thomas Jefferson dined alone.” Upon reaching the podium, Hoyt, with his typical modesty, quipped, “I’m nauseated.”

I’ve been asked why I chose this title for the lecture. As I have been out of full-time clinical practice for the past 15 years, there is nothing new I can tell you about clinical neuro-ophthalmology. Instead, I will dwell on some nonclinical issues.

TEACHING AND PassIONS

Almost all neuro-ophthalmologists teach. Why? For openers, I can’t disagree with Osler’s statement, “Your students and disciples will constitute your greatest honor” and Henry Adams’ comment, “Teachers affect eternity—one can never tell where their influence stops.” But William Parsons was justifiably undecided as to whether “we teach for altruistic reasons or to fortify our own narcissistic self-images.”

My vote goes to William Chambers, who taught neuro-anatomy when I was a medical student at Penn. It was before the use of slides, and he illustrated his lectures with blackboard drawings. His first lecture was on the anatomy of the thalamus, the second on the thalamo-cortical connections, and the third on thalamo-spinal connections. At the start of his fourth lecture, he told us it would be on thalamo-thalamo connections and turned to the blackboard. Just about everyone in the class softly groaned, but 125 groans got Chambers’ attention as he began to draw the thalamus. He turned around and said something like, “I guess you wonder why I’m telling you all this, which will have no benefit for you as practicing physicians. I am giving these lectures for the same reason I spend my life studying the thalamus. It PLEASES ME.” He then turned around and began to draw. The thalamus was his passion, and his justification had an impact on my career decision-making over the years.

The legendary gambler Nicholas Dandolos (Nick the Greek) said that his greatest passion was “gambling and winning.” His second greatest passion was “gambling and losing.” Warriors seem to share passions. Beowulf wanted “to die with a sword in hand, and to be transported to spend the whole of eternity eating, drinking beer, and fighting.” For Kipling, it was “women, horses, power, and war.” Of Churchill’s Boer War experience, he wrote, “Nothing was more exhilarating then being shot at and missed.” French Colonel Christian de Castries preferred “a horse to ride, an enemy to fight, and a woman to bed.”

When the notorious bank robber Willie Sutton was asked why he robbed banks, he allegedly replied, “That’s where the money is.” But in his autobiography he wrote that he robbed banks because he enjoyed it. He felt more alive when he was robbing a bank than at any other time in his life.

Rather curious passions were those of Oxford scholar Benjamin Jowett, who wished “to arrange my life in the best possible way, that I may be able to arrange other people’s,” and Anton Chekhov, who longed to “be idle and to love a fat girl.”

My passions are in accord with those of William Butler Yeats’ “continuous drinking of knowledge,” and H. G. Wells’ “editing someone else’s manuscript.” I would add family (a wife, 3 sons, and 6 grandchildren) and teaching.

RECEPTIVITY TO LEARNING AND PERFORMANCE

To be optimally receptive to learning, trainees should be relaxed. I never asked students or house officers serious questions in a group setting. I wanted them relaxed and unconcerned about being put on the spot. When alone with one of them, I have not hesitated to ask such questions because the wrong answer won’t be embarrassing.
That anxiety degrades performance became quite evident to me in an incident involving the late Peritz Scheinberg, the first chair of Neurology at the University of Miami and my first boss. Tired of having to teach the neurologic examination to every new group of rotating students, Scheinberg decided to make a teaching film of the examination. He selected the brightest fourth year medical student as the subject, and when he got to the mental status exam, he asked this young woman, who was about to take her internship and residency at Harvard, to subtract 7 from 100 serially. She was so nervous during the filming that she made numerous mistakes with a simple task that she would have performed easily in a relaxed state.

EFFECT OF MORALE ON PERFORMANCE

In 1965, after finishing my neurology residency, I entered the US Army and was soon sent to Vietnam as the first and only neurologist serving the allied forces. I was attached to a psychiatric unit and, given our unique expertise, we expected to be stationed in a Saigon hospital and housed in a nice villa. Instead we were sent to a remote hospital carved out of a jungle and rubber plantation. Psychiatric casualties appear to do better if hospitalized in a facility that simulates field conditions. If you take a young soldier who cracks up in the field, and put him in a nice clean, safe hospital with nurses dressed in white, and serve him good food, he won’t want to return to the field. But if you put him in our hospital with giant rats, spiders, snakes, and incoming mortars, he would regard the battlefield as being safer.

The living conditions for the Medical Corps at our Evacuation Hospital in Vietnam were terrible. Indeed, the non-physicians had better accommodations. Dr. David McK. Rioch, the head of neuropsychiatry at the Walter Reed Army Institute of Research, visited our unit to discuss our patients. He casually asked about our living and working conditions. We didn’t hesitate to ventilate about our lack of hot water for showers, lack of drinking water, and terrible food compared with what the enlisted personnel and nurses had. The more we complained, the more Rioch seemed pleased. He finally said gleefully, “They’ve read my study.” During the Korean War, he had studied the effects of morale on performance in all military units and found a direct correlation between high morale and optimal performance in all units except the Medical Corps. He concluded that physicians were so well trained, that no matter how bad their morale, they performed well. Thus, in a limited resource environment, the military didn’t regard Medical Corps morale as being an important consideration. Reluctantly, we agreed with the logic. We were working hard and efficiently despite our global dysphoria.

Years later, as an attending in a teaching hospital, I realized that Rioch was wrong. The performance measures he probably used for the Medical Corps were the number of patients seen and the mortality rate. But no matter how poorly a physician may feel, he or she will see all the patients that need to be seen and keep them alive if possible. What may be missing is compassion and empathy. It is difficult to be compassionate and engaged when feeling poorly or depressed. I noticed that when our residents were unhappy, they performed their basic functions but without compassion and personal interest. I thus became, to use a military term, a “morale officer.” When I would see obviously unhappy residents, I’d take them aside and attempt to determine the cause. I would then counsel them or send them to a professional.

PRESCRIPTIVIST OR DESCRIPTIVIST

I mentioned that I don’t ask serious questions to trainees in a group setting, but I do ask nonthreatening questions to illustrate a point. If a resident describes a patient’s “legs” as weak, I might say, “Define the leg.” The correct answer would be “the distal portion of the lower extremity beginning at the knee.” I was being a “prescriptivist” rather than a “descriptivist.” When I was a medical student at Penn and a neurology resident at Yale, if I said “leg” when I meant “lower limb,” I was publicly corrected. I might ask trainees to define “foot” and then point out that the Ohio Revised Code (the applicable law in the state) defines foot as “the terminal appendage of the lower extremity that includes the ankle joint, distal tibia, and fibula.” (It seems that the podiatry lobby prevailed with our state legislature).

A follow-up question might be, “Do subhuman primates, carnivores, and other creatures have feet?” Abraham Rabiner, the most prominent academic neurol- ogist in Brooklyn, a man who had retired to Miami in his mid 80s, said “no.” He had written an article in Brain in the 1920s contending that “the foot defines the extremity in which the big toe forms the fulcrum in walking.” If so, only humans have feet. A further question might be, “Why does the foot only plantar flex or dorsiflex, but never extend?” This question often provokes an interesting discussion.

PROFESSIONALISM

Professionalism may clash with reality concerns and personal safety. In Vietnam, we not only treated our wounded soldiers but also cared for our enemies, the Viet Cong (VC). Wounded VC captured by American soldiers were often taken to our hospital, and we gave them our best care.

I recall an American soldier who was unconscious with a bloody head wound. An x-ray revealed a hand grenade in his head that hadn’t exploded because the firing lever was tamponaded by the brain and the hematoma. The frontal lobes seemed totally destroyed. We knew that
ultimately the grenade would explode. Should we evacuate the hospital and try to remove it? We had only three neurosurgeons in the whole country. Was it prudent to put one at risk and risk the lives of operating room personnel to save the life of someone who, at best, would be in a vegetative state? A pragmatic decision was made.

Professionalism may also clash with personal animosity. At the end of World War II, the distinguished Norwegian neurologist Sigvald Refsum (of Refsum syndrome) was asked to examine Vidkun Quisling, the former Norwegian head of state who had been imprisoned for collaborating with the Nazis during their occupation of Norway. Professor Monrad-Krohn, the senior neurologist in Norway, suspected some type of brain disease must have led to such treacherous behavior. Taken in prison garb to Refsum’s office for a neurologic examination, Quisling greeted Refsum and extended his hand. Refsum refused to shake it. The examination was normal, and Quisling was ultimately shot by firing squad. According to Refsum’s obituary, for the remainder of his life he felt remorse for letting his personal revulsion interfere with a basic element of professional behavior—the shaking of a patient’s hand.

Professionalism is better modeled than taught. We saw the model in our faculty at Penn. During rounds, I. S. Ravdin, the chair of surgery, always sat at the patient’s bedside, showing empathy and concern. On rounds, Francis Wood, chair of medicine, once led us into a patient’s room and immediately placed his thumb on the patient’s radial pulse. Then he had us leave the room and asked, “What did I do wrong?” We all replied, “You don’t take a pulse with your thumb,” to which Wood responded, “You mean that I can’t tell the difference between my pulse and the patient’s pulse? What I did wrong was not introducing myself and you to the patient and not telling him what we were going to be doing.”

When I finish examining a patient on resident rounds, I make it a point to replace the patient’s socks and to put the bed, side rails, and IV pole back to their original positions. The resident and students get the message.

PUBLISHING

I want to help you get your articles published. Follow the 1881 rules of John Shaw Billings: 1) have something to say; 2) say it; 3) stop. Another suggestion is to avoid using the passive voice. Do not write “It was felt that the patient was weak,” but rather “The patient was weak.” The passive voice should only be used in the Methods section, where “The cats were then sacrificed” is preferable to “We then killed the cats.” You can find many additional suggestions in *Neurology* 1996;46:298–300.

If you describe a new syndrome, it would please your parents and grandchildren to see your name eponymized. When Milton Shy, as chief of the Neurologic Institute at the National Institutes of Health, described a newly recognized muscle disease as “central core disease,” that apt designation stuck, prompting Shy to say that if you wanted an eponym, be sure to give diseases names that have long Latin descriptors such as “polioencephalitis hemorrhagica superioris” (which became Wernicke encephalopathy), “angior- keratoma corporis diffusa universale” (which became Fabry disease), or “heredopathia atactica polyneuritiformis” (which became Refsum syndrome).

CAUSALITY

Samuel Johnson remarked, “Physicians seem to confuse subsequent for consequent.” The Latin expression *post hoc ergo propter hoc* describes this logical fallacy, which trainees should be taught to recognize and avoid. I usually provide some examples. The swine influenza vaccine of the late 1970s was said to produce Guillain-Barré syndrome, and billions of dollars in lawsuits followed. Arthur Asbury finally conducted an epidemiologic study showing that Guillain-Barré syndrome incidence after the vaccine was merely at its baseline rate. To dispel the notion of “post-vaccination crib death,” I tell the story of the woman who, when taking her infant for vaccination and finding a long line in the physician’s office, decided to go shopping and come back later. While in the store she took her eyes off the baby for a few minutes and then discovered that the baby was dead in the stroller. Had the baby been vaccinated as planned, there would have been little doubt in many minds that the vaccine had caused the death.

THE GOOD OLD DAYS

We are living in bad economic times, but did we think we were living in good times 5, 10, 20, or more years ago? When were “the good old days?”

In 400 BC, Socrates noted that children had bad manners, did not rise when an adult entered the room, contradicted their parents, and intimidated their teachers. In 55 BC, Cicero recommended that “The budget should be balanced, public debt should be reduced lest we become bankrupt, and people must again learn to work instead of living on public assistance.”

The first century Roman poet Ovid described mankind’s decline from the Golden Age, when man had uncorrupted reason and pursued good, to the then extant Iron Age, when fraud, avarice, and force had replaced truth, modesty, and shame. The 13th century Castilian monarch Alfonso the Learned immodestly remarked, “If God in his wisdom had only consulted me before embarking on His creation of the world, I would have suggested something simpler.” The aging Jefferson, decrying the deterioration of American society, wrote to John Adams, “They’ll never
know what we had.” Somewhat later, the newspaper columnist Franklin Pierce Adams (1881–1960) mused, “Nothing is more responsible for the ‘good old days’ than a bad memory.” Artie Shaw (1910–2004), the oft-married clarinetist and band leader, astutely stated, “These are the good old days the next generation will hear so much about.”

Medicine is particularly criticized because of its departure from the good old days. A wise contemporary has noted, “The old time doctor who waited by the patient’s bedside while he died was held in higher esteem than the physician of today who provides a prescription, and then absents himself while his patient recovers.”

In a 1907 issue of the Journal of the American Medical Association, a writer stated, “It’s perhaps fair to say that the average physicians of today have too exalted an idea of the science of medicine and too pessimistic a view of the art of medicine. Too many physicians sit back in their easy chairs, waiting for a laboratory to solve a problem whose solutions can often be just as accurately reached by the use of their own eyes, ears, and fingers.” Dr. Francis Peabody (1881–1927) at Harvard was particularly critical of his contemporaries, stating that “The laymen of the older generation feel that something is lacking, like warmth, sympathy, and understanding, and want to return to the good old days of the general practitioner.” He went on to say, “To put it more bluntly, current medical school graduates are ‘too scientific,’ and do not know how to take care of patients.” Joining the self-criticism in 1938, the physician-scientist Isadore Snapper wrote, “House staff have the tendency to consider taking the history and performing the physical examination as an old fashioned method, which should be declared obsolete. These souls believe that they will stumble upon the diagnosis if only the expensive machinery of the clinical laboratory would send them sufficient report slips.”

To put this matter into perspective, one of my heroes, UCSF Nobel Laureate J. Michael Bishop, noted, “It seems we have always been in troubled times, no matter what era of recorded history it might suit your fancy to sample.”

This assessment puzzles me because I do believe things are getting worse, but perhaps since at least 400 BC. How could there always have been “the good old days,” even in “the good old days?” Perhaps Logan Pearsall Smith (1865–1946), the essayist and critic, was correct when he said, “The denunciation of the young is a necessary part of the hygiene of older people, and greatly assists the circulation of the blood.”

**SURVIVAL SKILLS**

Given that things are bad and are destined to worsen, I’ll provide you with some nuggets of advice. A simple experience affected my reactions to many irritations. While at the University of Miami on an oppressively hot August day in the 1970s, I entered a crowded hospital elevator in which a posted sign read, “It is illegal in this elevator to ask ‘is it hot enough out there for you?’” We were all deprived of “basic elevator talk,” and I realized how our moods were influenced by the weather, and how the accepted custom of complaining about it may actually enhance dysphoria. I then decided that the weather, be it a blistering summer Miami heat or a Cleveland blizzard, should be ignored, as long as the car starts and the roads are driveable. There is a slight downside to this philosophy. You can never say, “It’s a nice day,” because that implies that some days are not nice. I never comment about good weather, and when someone does (rarely in Cleveland), I may say something like “I wouldn’t know, I’ve been inside all day.” Or, I might relate the elevator anecdote.

G. Gordon Liddy, of Watergate infamy, felt wronged by our judicial system. In his biography, he noted being often asked whether he was “bitter” and he replied, “Bitterness can only be experienced if one simultaneously indulges in self-pity, and self-pity is the most useless expenditure of psychic energy I can imagine.” When I find myself aggrieved about something for more than a few days, I return to that Liddy remark, and try to get over it. Rabbi Kushner, author of *When Bad Things Happen To Good People*, said, “Expecting the world to treat you fairly because you are a nice person is like expecting the bull not to attack you because you are a vegetarian.”

To paraphrase Osler’s 1903 address to the University of Toronto medical graduates, “I propose to tell you the secret of life as I have seen the game played, and as I have tried to play it myself. I propose to give you the Master Word. Though a little one, the Master Word looms large in meaning. It is the open sesame to every portal, and the great equalizer in the world. The average person among you will be made bright, the bright person brilliant, and the brilliant student unsurpassable. With the Master Word in your heart, all things are possible. It is directly responsible for all advances in medicine during the past twenty-five centuries. The Master Word is WORK!”

I try to follow the advice of former mentor Lewis Mumford (1895–1990): “Nothing is sacred but the integrity of your own mind. Your main need is to have a firm inner center based on your own identity and your own work, an affirmative self-respect that no institution, no outward circumstance, can violate: your own yes and no.”

We are dealt a hand and we should play it to the best of our ability, without wasting the time or the energy to complain about the cards, the dealer, or the rules of the game. Just play out the hand.
Robert B. Daroff, MD
Pioneer of Ocular Motor Research

Jonathan D. Trobe, MD

Robert B. Daroff, MD was born in New York City and, except for a 2-year hiatus at military school in Georgia, attended public school there. He left high school early to start undergraduate education at the University of Chicago, but transferred to the University of Pennsylvania, where he served as editor-in-chief of The Daily Pennsylvanian, the college newspaper.

He entered the University of Pennsylvania Medical School bound for psychiatry, but a fascination with internal medicine and an exposure to potent role models in neurology guided him toward neurology. A chance encounter with David Cogan’s little masterpiece, The Neurology of the Ocular Muscles, led to his becoming the local expert on eye movements while he was a resident in neurology at Yale University. To further his knowledge in this field, he undertook a 3-month elective rotation with J. Lawton Smith, MD which gave him exposure to the talented cadre of neuro-ophthalmologists at the University of Miami and sealed his decision to become a neuro-ophthalmologist.

After serving a 2-year stint as a neurologist in the United States Army, he became a neuro-ophthalmology fellow under the direction of William F. Hoyt, MD at the University of California-San Francisco and later joined the faculty at the University of Miami. There he began to document the trajectories of normal and abnormal eye movements with Louis Dell’Osso, PhD and other systems control wizards. He left Miami in 1980 to become chair of the neurology department at Case Western Reserve University in Cleveland. His strong support of ocular motor research led to the establishment of the Daroff-Dell’Osso Ocular Motor Laboratory at Case, from which seminal contributions to the understanding of eye movements continue to emerge.

From 1987 to 1997, he served as editor-in-chief of Neurology, the official journal of the American Academy of Neurology. An authority on the management of headache, he has looked after members of the royal families in Saudi Arabia and other Persian Gulf states. After he stepped down from the chair position, he served as chief of staff of University Hospitals-Cleveland and is currently Associate Dean for Development at the medical school.

He has held virtually every leadership position and received every honor in American neurology and neuro-ophthalmology. He is one of the founders of the Rocky Mountain Neuro-Ophthalmology Society, the predecessor of the North American Neuro-Ophthalmology Society (NANOS). Recognizing the value of applying engineering principles to the analysis of eye movements, he has trained many of the ocular motor investigators at major university centers around the world.

This interview took place at Lake Tahoe, Nevada, on February 23, 2009.

JDT: I know you were born in New York City, but I found it odd that you left elementary school to go away to military school...

RBD: Yes, I went to Riverside Military Academy in Gainesville, Georgia, when I was 10 years old.

JDT: Why military school?

RBD: My family thought it was best that I get some discipline.

JDT: You didn’t have discipline?
RBD: I thought I did, but I got a whole lot more in military school. When I got back to school in New York, I remember the teacher calling off the roll, and everyone would answer “Yeah,” but when she came to me, I said “Yes, ma’am.” The class laughed. I still say “Yes, ma’am” and “Yes, sir.”

JDT: And in spite of this stiff training, you chose later to go to college at the ultra-liberal University of Chicago. Why?
RBD: There was a study to see how high school kids would do if they came to college early. Four colleges participated: Harvard, Yale, Columbia, and the University of Chicago. You would get a scholarship if you passed the entrance exam, which I took in my sophomore year. I didn’t make it, but the University of Chicago agreed to take me if I would pay the tuition. I wanted to go, so my parents agreed and I enrolled at age 16.

JDT: Why would you go off to college at such a young age? Had you outgrown high school?
RBD: I was ambitious. I was accepted to college. Why not go?

JDT: What was it like to go to college so young?
RBD: The summer before I started, I taught myself to smoke. I thought it was a “mature thing.” I worked as a beach boy at the (New) Jersey shore, and every evening I would go out on the dock and inhale and cough. It wasn’t easy, but I was becoming a man.
JDT: Why the Jersey shore?
RBD: My father, Charlie Daroff, was one of four brothers who owned H. Daroff and Sons, a well-known Philadelphia company that made Botany 500 clothes. We lived in New York only because my father ran the New York office. Every summer the family got together in southern New Jersey—at Ventnor or Margate, on the beach.

JDT: How did the year at the University of Chicago turn out?
RBD: It was fantastic academically, and I developed all sorts of interests in things like transcendentalism, Hemingway, Hawthorne. But when I would come home for breaks, I wasn’t really communicating with my parents or their friends. I honestly felt that this college education was not preparing me for my family’s circle of friends. When they got together, it wasn’t existentialism that they talked about. I felt out of touch. Also, there was the girl situation. I was a 16-year-old kid without a car in Chicago. I decided I wanted to be around the family in Philadelphia, so I transferred to Penn (the University of Pennsylvania).

JDT: Did Penn give you credit for the courses at the University of Chicago?
RBD: Not really. They accepted me as a freshman, provided I took one more course. So I took a social studies course at the summer school of the University of Chicago. My roommate happened to be Carl Sagan.

JDT: Before he became the Carl Sagan…
RBD: Yes, of course. I knew he was the smartest person I’d ever met but who knew he’d go on to be Carl Sagan. Besides being smarter, he was a year older and more mature than I was. The other thing that happened that summer was that I got into Freud, especially his book Civilization and Its Discontents. It explained why I was unhappy. The way I interpreted this book was that we are sexual creatures and the only way to get rid of this strong sexual desire is sublimation, which was not really adequate. So we were destined to be unhappy.
JDT: Did this incline you toward psychiatry?
RBD: I was hooked on being a psychoanalyst. But I started a regular college life at Penn, with fraternities and girls—all the things I hadn’t had in Chicago.

JDT: What do you recall of those undergraduate years?
RBD: Fraternity life was vital. The fraternities had lists of all the students at Penn, and next to each name was either the letter P, C, or H—Protestant, Catholic, or Hebrew. This was 1953. There were gentile fraternities and Jewish fraternities. Some gentile fraternities—the highfalutin ones—did not take Catholics. There were absolutely no Jews in the gentile fraternities. The Jews were in the 13 Jewish fraternities. There was only one black student in my class (he became a successful orchestral conductor) and he was in a Jewish fraternity.

JDT: You pledged?
RBD: Yes, at Sigma Alpha Mu, in my freshman year. They told me that to be admitted, I had to go out for an activity. I told them I was pre-med and didn’t have time for other activities. They said you have to do something. I wasn’t a good enough jock, so I decided to go out for the newspaper—The Daily Pennsylvanian. Trying out was called “heeling.” I was forced to heel. But I made it on to the newspaper. And I became editor-in-chief in my senior year, an experience that became very important for my later life.

JDT: What did you do for The Daily Pennsylvanian?
RBD: I put the paper to bed every fifth night, copyediting. I organized. I commissioned stories. I wrote stories. I covered a story about an important skull being discovered in Africa that had anthropologic significance. I called up Loren Eiseley, a big professor at Penn, and he invited me over to his office and explained for 2 hours why this was such an important finding. I also remember interviewing Lewis Mumford, the writer and city planner, about why we should give up nuclear weapons. He asked if he could see my article before it was published. I said “Yes, sir.” He rewrote it completely. It appeared under my byline—the best thing I have ever written! Mumford discovered Melville’s Moby Dick. It was just a whaling story until he analyzed it. Fantastic. After that experience, I took a graduate course that he taught.

JDT: How did you do academically at Penn?
RBD: Not well. I settled for Cs. I never studied. I spent all my time either at the newspaper or playing Hearts at the fraternity.

JDT: And after graduation?
RBD: I was accepted to Penn Medical School. With my crummy grades, it was only the newspaper editorship that got me in.

JDT: What happened at Penn Medical School?
RBD: It was complicated. From being a big man on campus, and an American Civilization major, I was suddenly among science majors who were smarter than I was. I didn’t do well in the first year. That Fall my father died and I got depressed. I consulted the student health psychiatrist and found the sessions helpful. I wanted to continue, so they recommended full psychoanalysis. I wound up as a patient of Aaron T. Beck (father of Roy Beck, MD, PhD and later winner of the Lasker Award). What luck that was! He was getting disenchanted with psychoanalysis and shifting into cognitive therapy. I was there for the transition.

JDT: Weren't you also doing research in psychiatry at the time?
RBD: Yes, a Penn professor thought that essential hypertension was due to inverted hostility: you were really angry, but you didn’t let it out, and therefore you became hypertensive. He thought you could prove this by analyzing the dreams of hypertensive patients, which should be hostile. I went around to hospitals and clinics collecting dream information and scoring it for hostility. The theory
turned out to be wrong. Beck wondered whether depressed people were hostile in their dreams, a prediction of psychoanalytic theory. Much to his surprise, it turned out that they were as depressed in their dreams as in their waking life. I think it was this finding that finally took Beck out of psychoanalysis.

JDT: You have told me that an accidental event in medical school had a major effect on your life…

RBD: Yes, meeting Jane. She had transferred to Penn from Vanderbilt University in her junior year. She was standing outside a phone booth with my lab partner, who was waiting for me to finish a phone call. I came out of the booth and Jane went in to make a call. I asked my lab partner later if he was interested in her and he said sure, but he found out that she belonged to a Jewish sorority. He said that his Catholic mother would kill him if he brought home a Jewish girl. So I said, “Well, that is not my problem.” We dated but my understanding was that you do not get married while you are in psychoanalysis. I eventually mentioned it to Beck and he said, “Where is that written?” He had met her and he thought she would be great for me—beautiful, smart, calm, likeable. We got married in my junior year in medical school. In December of 2009, we will have been married 50 years. By the way, I still keep up with Beck.

JDT: If you were bent on psychiatry, how did you get sidetracked to neurology?

RBD: Another accident. When I rotated through internal medicine as a third year medical student, I found that this stuff was really good. I realized I couldn’t give it up. Then I ran into some wonderful role models in my neurology rotation and that did it—away from psychiatry and into neurology.

JDT: Who were these role models?

RBD: Jim Toole, later neurology chair at Bowman Gray, John Bevilacqua, Gabe Schwarz, and Abraham Ornstein. After I finished my neurology rotation, I spent a month cutting brains in the mornings—learning neuroanatomy—and the afternoons in Toole’s office seeing patients with him.

JDT: Who taught you how to cut the brain?

RBD: Nobody. You cut vertically or you cut horizontally. I used an atlas.

JDT: So internal medicine plus psychiatry yielded neurology for you.

RBD: Yes, every patient with chronic neurologic disease has psychiatric problems.

JDT: What was neurology like when you started?

RBD: I started in 1962. There wasn’t any imaging—CT came in 1972 and MRI in 1982. There wasn’t much treatment either. We had phenytoin and phenobarbital and myosoline for epilepsy and ergotamines for headache. Making the diagnosis—the thought process—that is what turned me on.

JDT: You went to Yale for neurology residency. How come?

RBD: Penn neurology was in transition. Jefferson was a great program, but Alpers, the chair, would make rounds at 5:30 in the morning. That may have satisfied Norman Schatz, who took his residency there, but not me. Harvard required another year of medicine. I did not want to live in New York. So that left Yale, a terrific program.

JDT: Who influenced you at Yale?

RBD: Gil Glaser, the neurology chair, and Lew Levy at the VA were very impressive. But it was during my internship at Philadelphia General Hospital that another accident occurred that altered the course of my life…. 

JDT: And that was….

RBD: One of Jane’s friends had married an ophthalmology resident at Penn. One night we went to visit them, and he had Cogan’s book, The Neurology of the Ocular Muscles, lying open on his desk. I asked if that
was a good book, and he said yes. So I bought a copy. A year later, as a first-year neurology resident, I was making rounds at the VA at Yale with Levy and we had a patient with supranuclear ophthalmoplegia. Lew said, “I don’t really understand this. One of you guys is going to have to read about eye movements and present it to the group.” It fell to me to be the one. So, for the entire 3-month rotation, I read Cogan, Kestenbaum, Holmes, and Bender. Then I wrote a paper for the group on eye movement control. There I was, knowing more about eye movements than anyone else at Yale. There was no one doing neuro-ophthalmology at the time.

**JDT: Where did it go from there?**

**RBD:** I decided I had better study under someone who really knew about eye movements. I wrote Walsh. He replied that he was sorry, but neuro-ophthalmology was a subspecialty of ophthalmology. Marvin Sears, the ophthalmology chair, suggested I contact a former co-resident of his from Wilmer—Lawton Smith. And Lawton said “Yeah. Come.” So I spent 3 months of my second neurology residency year with him in Miami.

**JDT: How was the time with Lawton Smith?**

**RBD:** Wonderful. I realized that I did know something about eye movements, but I learned more. I decided to become a neuro-ophthalmologist.

**JDT: But first you had to serve your military duty.**

**RBD:** Yes, I spent 6 months as a U.S. Army neurologist at Fort Knox, Kentucky. Then I was sent to Vietnam for a year as the first and only Army neurologist in the country. I was supporting a psychiatric unit. We were sent to a hospital in the jungle. Why the jungle? If you take a psychiatric casualty and put him in a nice clean hospital with good food far away from the fighting, he is not going to want to get better. Put him in our jungle hospital—with snakes and rats and giant spiders and awful food and danger—and he will want to get right back in action.

**JDT: What could a neurologist like you possibly contribute?**

**RBD:** I took care of 18 soldiers with cerebral malaria. And kids who had fits, faints, and headaches. That part was not so different from a stateside neurology practice.

**JDT: And then back home to the States…**

**RBD:** …to Letterman General Hospital in San Francisco, to serve out my last months of army duty. There I met a young physiatry resident named John Susac. He rotated on neurology with me and decided to become a neurologist. Later, when I was editor of *Neurology*, I asked him to write a paper on his syndrome of retinal, ...

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**FIG. 8.** Captain Daroff, United States Army, Fort Knox, 1965, with Jane before going to Vietnam.

**FIG. 9.** In Vietnam, 1966.
cochlear, and cerebral manifestations. I insisted he call it “Susac syndrome” and he did.

**JDT:** And then you moved across town to spend a year’s fellowship in neuro-ophthalmology with Bill Hoyt at the University of California, San Francisco. What of that?

**RBD:** Hoyt is to neuro-ophthalmology what Boswell was to Samuel Johnson.

**JDT:** A scribe?

**RBD:** Yes. For every patient we saw, he had a card. Hoyt knew everything. His neuro-ophthalmology was different from Smith’s. Smith’s was an office practice. Hoyt’s was basically rounds on the inpatient neurology and neurosurgery services. We had permission to examine without formal consultation any patient on those services. As the senior fellow, I would go around every afternoon and decide which patients we would present the next day to Hoyt. I would call him at home late in the evening. After only one ring, he would always answer: “Hoyt here!” He often dismissed as uninteresting the patients I suggested. Rounds began at 7:30 in the morning. If you were late, it was a disaster. To avoid being late, I met him for breakfast every morning at 7. He had dug into his reprint file and brought reprints on the patients we were going to discuss. But he never let go of those reprints! You had to get your own version.

**JDT:** Was there any downside to the experience?

**RBD:** We did not have control of our patients. I did not like just giving opinions—what I call “service neuro-ophthalmology.” I wanted to go to a place where they had neuro-ophthalmologists doing that, so I could do general neurology and specialize in eye movements. And where was such a place? The University of Miami. Ed Norton had been a neuro-ophthalmologist. Smith was there with John McCrary, Joel Glaser, and Nobby (Noble) David. My referrals came from them.

**JDT:** When did you get there?

**RBD:** I arrived in 1968 with a joint appointment in neurology and in ophthalmology at the Bascom Palmer (Eye Institute). Nobby David needed help in neurology at
the Miami VA, so I went there. But another important accident happened before I got there.

**JDT:** What was that?

RBD: Peritz Scheinberg, then the neurology chair at Miami, wrote me a letter before I arrived asking me to spell out the systematic research I was going to do when I joined the faculty. I wrote back to say “Neuro-ophthalmologists are phenomenologists. We don’t do systematic research. We observe and write down what we see.” At that point, I had already written 13 papers, only one of which was an actual research paper. Scheinberg wrote back: “Everybody in my department has to do systematic research. Find something.”

**JDT:** So what did you do?

RBD: Someone had written a paper showing that eye movements could predict phenytoin blood levels. But no recordings. I decided I would quantitate that phenomenon with DC oculography.

**JDT:** How did you know about DC oculography?

RBD: I forget. But somehow I knew enough to write a proposal. Then Nobby David wrote me that the VA had research money and I could have it, but I had to spend it before the year ended or we would lose it. I was advised to buy a Beckman 8-channel DC oculography machine. My first study was a recording of saccades in normal subjects simultaneously from each eye separately, which no one had ever done. That was a simple study. If I was to go further, I needed someone who really understood the machinery. That was Lou Dell’Osso. He had spent time studying eye movements with Larry Stark at the School of Optometry at Berkeley. Lou had written his PhD thesis in biomedical engineering on his own congenital nystagmus. He had been recruited by the biomedical engineering department at Miami, but they had no eye movement equipment. Here I was with equipment but no knowledge. So we became a team. We have collaborated for 40 years. He enabled me to be more than a dilettante.

**JDT:** That collaboration was to become the Daroff-Dell’Osso Ocular Motor Laboratory, first in Miami and later in Cleveland.

RBD: Right. We studied normal and abnormal eye movements. We were part of the training grant in neuro-ophthalmology that supported the Glaser fellows for 11 years. Nearly all our fellows wrote papers with us. Todd Troost, a neurologist trained by Hoyt in neuro-ophthalmology, joined us as a full-time fellow for two years and later joined our faculty. Larry Abel and other PhD engineers came on to do postdoctoral training, and it became a thriving lab.

**JDT:** What did you discover?

RBD: The metrics of normal eye movements. The waveforms that distinguish congenital, vestibular, and gaze-paretic nystagmus based on the slope of the slow phase. We studied latent nystagmus and coined the term...
“saccadic intrusions” and catalogued the various forms. In our normal saccade study, we found that with large saccades, one eye would land on target, the other eye would fall short—and drift or slide into the target. “Glissade” is the skiing and ballet term for sliding. Ron Weber, my collaborator, was a musician, so he suggested we apply it. I think we became famous for that!

JDT: How did your work compare with what was being done at other ocular motor laboratories?

RBD: We established the linkage between the engineer and the clinician in eye movement analysis. David Robinson and David Zee and others did similar work later.

JDT: After 12 years in Miami, you left to go to Case Western Reserve in Cleveland …

RBD: I wanted to be a chairman of a neurology department.

JDT: What happened to the ocular motor research when you moved to Cleveland?

RBD: We were even more productive. As department chair, I was able to support it. John Leigh and Mark Walker, two terrific people, later joined us.

JDT: You were the Gilbert Humphrey Professor and chair of the department of neurology at Case for 13 years. Was it fun?

RBD: It was initially—recruiting and building a department from a division of medicine. Joe Foley, a great neurologist, had left the division head position 3 years before I came, and by the time I arrived, there was practically no one on the faculty. As a division, it was impossible to recruit anyone of substance. Also, the residency was on probation. Fortunately, we became a department when I arrived and got off probation within a year. I managed to build up a good group or residents and faculty, but we were losing money. I began to tire of always thinking about money. When you come as a new chair, you are at the trough—you get help from the dean. Ten years later, you are far away from the trough. Then it is time to bring in someone new to be a favorite son.

JDT: During your chairmanship, you were editor of Neurology—the “green journal.” Let us talk about that.

RBD: Russell DeJong founded the journal in 1948 and stayed on as editor for 23 years. Then the editorship became a 10-year term. Lewis Rowland followed DeJong, and I became the third editor. My appointment came from another accident.
JDT: This would be accident number 5, but who is counting.

RBD: OK. When I was Hoyt’s fellow, Fred Plum, then chair of neurology at Cornell, got delayed in San Francisco on a flight to Japan. He decided he would spend the day making rounds at UCSF. Our neuro-ophthalmology bunch was the only group making rounds. We decided to present a woman with encephalitis. Her husband at first refused to have us come in. So Plum imperiously barges in and tells the husband that he—Plum—has been summoned from New York to render a special opinion which will improve her care. The husband starts to cry and says certainly. Years later, when Plum was a visiting professor in Miami, I reminded him of that. We must have developed a relationship, because, as editor, he appointed me to the editorial board of the Archives of Neurology, then the official journal of the American Neurological Association, but published by the American Medical Association. Some years later, Plum became angry at the AMA for interfering with his editorial decisions. So he and the entire editorial board quit, and we started our own journal, the Annals of Neurology. When he later became head of the search committee for the next editor of Neurology, he came up to me at a meeting in Germany, grabbed my arm, and said “Daroff, how’d you like to be editor of Neurology?” But aren’t there qualified candidates in the search, I asked. Plum replied, “Look Daroff, this is what is good for American neurology. They aren’t. You are. Do you want the job?” I meekly said yes.

JDT: How did you change the journal?

RBD: I inherited a great journal from Rowland. We quadrupled the number of published manuscripts, condensed them, shortened the delay from submission to publication from a year to about 4 months. I compulsively copy-edited—my experience at The Daily Pennsylvanian. I still get cross over a split infinitive. Some of that I attribute to Hoyt, who was a very tough language critic and wrote well himself.

JDT: Of all the honors and awards you have received, which one stands out?

RBD: President of the American Neurological Association, the senior society of neurologists in the United States. Founded in 1875, it is the oldest neurologic association in the world.

JDT: Are you one of the founders of the Rocky Mountain Neuro-Ophthalmology Society, which later became the North American Neuro-Ophthalmology Society (NANOS)?

RBD: Yes. Tom Carlow was a neuro-ophthalmology fellow with my colleague Joel Glaser at Miami. Tom moved to New Mexico. He and Joe Bicknell, who liked to ski, started the annual meeting at a ski resort. Carlow, Bicknell, Glaser, Hoyt, and I were the original faculty.

JDT: Besides being a neuro-ophthalmologist, aren’t you something of a headache specialist?

RBD: Yes, that came from another accident. In Miami, Peritz Scheinberg considered all headaches that did not have structural causes to be psychogenic. Nobby told all his headache patients that he solved his own headaches with a thimble full of Scotch. A lot of headache patients were being sent to ophthalmologists at Bascom Palmer because people thought the eyes had something to do with headache, which they rarely do. Those patients were referred to me. Besides, I was well trained in headache because Lou Levy at Yale had been trained by Harold Wolff. I liked treating headaches. Later, when I was in Cleveland, I got a call from Neil Raskin, a headache specialist at UCSF, who was looking for more academic rigor in that field. He asked me to take a leadership role in the American Headache Society, which I did.

JDT: You have also taken your headache skills abroad.

RBD: Yes, a daughter of the head of state in United Arab Emirates had bad headaches and had been seen by several neurologists around the world. They finally found FIG. 13. In front of the portrait of King Abdul Aziz Al Saud (Ibn Saud), the first Saudi king, in royal palace during a visit to Riyadh, Saudi Arabia, as “neurologist to the royals,” 1998.
me. She had severe migraine. I flew over with some DHE 45 and she got better. The sheikh’s personal physician began inviting me back. One day he notified me that I would be getting a call from the head of the Bahrainian medical society and that I should accept their invitation to take care of the queen. I did. And then I got on the Saudi bandwagon and have made over 20 trips to take care of various members of the royal family. The neurologic problems expanded, and I would take over other experts—a movement disorders person, a cardiologist—whatever I needed.

JDT: You are arguably most famous to young neurologists and otolaryngologists for the Brandt-Daroff positioning exercises. How did those come about?

RBD: Thomas Brandt finished his neurology residency at the University of Freiburg in the early 1970s under the legendary Professor Richard Jung. Thomas was interested in the vestibular system and published excellent papers during his residency. Thomas developed a contact with Bill Hoyt who recommended that he visit me at our Miami VA laboratory. He came and we bonded personally and professionally, as did our wives and children, over the ensuing years. Thomas discussed the treatment he had developed for benign paroxysmal positional vertigo, and I encouraged him to get more data prior to publishing.

We ultimately published it together in 1980 with Thomas as first author. It was his idea and study; I was merely an encouraging facilitator and scribe. The Brandt-Daroff exercise was the first and only treatment for over a decade, until Semont and Epley separately published their maneuvers, which have the distinct advantage of being a single “liberation” in the office, rather than our repetitive home exercises. But if the Epley and Semont maneuvers fail, the only alternative is the Brandt-Daroff exercise, which is then usually successful.

JDT: When you left the neurology chairmanship, it was for another administrative role?

RBD: As chief of staff at University Hospitals, Case Medical System. It was a good job, although a bit
frustrating. There was tension between the administration of the hospital system and the doctors. I had to mediate between them. The administration paid my salary and wanted me to be their person. But because I am a doctor, the medical staff thought I should be their person. It was hard on me. Eventually, new administrators were hired and they decided they wanted an MBA person in my job, so I moved on to become vice dean for education at the medical school.

JDT: And now?
RBD: I am the associate dean for development at the medical school, which means that I advise the fundraisers—I tell them who could be the benefactors.

JDT: Looking back on this interesting and productive professional life, what are you most proud of?
RBD: I trained a lot of very bright people. I hope it will be said that I was a good teacher.
Isolated Bilateral Ptosis as the Only Ophthalmologic Sign in the Fisher Variant of Guillain-Barré Syndrome

Fisher syndrome (FS) is a variant of the Guillain-Barré syndrome (GBS) that is typically characterized by the acute onset of the triad of ophthalmoplegia, ataxia, and areflexia (1). To our knowledge, bilateral ptosis as the only ophthalmic finding in FS has only been described only once before (2).

A 48-year-old woman reported distal numbness in all four limbs and unsteadiness of 2 days’ duration. Two weeks before presentation, she had experienced an upper respiratory tract infection with a sore throat. Her medical history was otherwise unremarkable.

Neurologic examination of the cranial nerves was normal. There were no pupillary defects, ptosis, abnormal eye movements, or nystagmus. Muscle strength was normal. Sensory examination showed a decrease in light touch and pinprick in both hands and feet, with normal vibration and joint sense in the limbs. She had mild gait ataxia. Limb dysmetria was absent. She had no dysdiadochokinesia or rebound phenomenon. Gait was slightly unsteady but not wide-based. Stride and arm swing movements were normal. Deep tendon reflexes were absent.

A complete blood count was normal, as were levels of serum electrolytes, glucose, C-reactive protein, and vitamins B6 and B12. Blood tests of coagulation and renal and thyroid function were normal. Lumbar puncture yielded a normal opening pressure and 3.9 mmol/L glucose, 0.55 g/L protein, and 6 leukocytes. Results of tests for human immunodeficiency virus, herpes simplex virus, varicella zoster virus, cytomegalovirus, Epstein-Barr virus, and Borrelia burgdorferi infection were negative in blood and cerebrospinal fluid (CSF). A paraneoplastic antibody screen showed negative results. CSF sent for anti-GQ1b IgG antibody measurement was lost.

Four days later she returned because of increasing dysesthesias and unsteadiness. Bilateral ptosis was now evident with pupils of normal size and reactivity (Fig. 1). Eye movements were normal, and the eyes were aligned. She had no facial weakness, slurred speech, or swallowing difficulty. Muscle power was decreased in all 4 limbs (Medical Research Council grade 4). There was marked extremity ataxia and such severe gait ataxia that the patient could not ambulate without holding on to the furniture.

Results of brain MRI were normal. Electrodiagnostic studies, performed 6 days after onset of symptoms, showed normal motor and sensory conduction velocities in upper and lower limb nerves, normal ulnar sensory nerve action potential amplitudes, and only slightly diminished sural sensory nerve action potential amplitudes (2 and 7 μV). Compound muscle action potentials amplitudes of tested motor nerves were moderately diminished (abductor digiti quinti 5.3 mV and extensor digitorum brevis 3.6 mV). In the left median motor nerve, partial conduction block was present (9.6 and 6.4 mV after distal and proximal stimulation, respectively). F wave latencies were normal in the median nerve but could not be elicited in the ulnar and peroneal nerves. The H-reflex over S1 could not be elicited bilaterally.

A 5-day course of 0.4 g/kg/day intravenous immunoglobulin was given, during which neurologic symptoms started to resolve. Ataxia diminished and muscle power returned to normal in less than 2 weeks. The ptosis started to improve during the same period. Six weeks later mild bilateral ptosis was the only residual neurologic finding. At 3 months after disease onset, the ptosis had resolved and deep tendon reflexes had returned. Anti-GQ1b IgG antibody was negative at this time.
Although bilateral ptosis was the only ophthalmologic finding in this case, the numbness, areflexia, ataxia, electromyography/nerve conduction velocity results, and clinical course supported the diagnosis of the Fisher variant of GBS. Since the original description of this syndrome in 1956 (1), there has been a continuing debate about the site of the lesion. Fisher (1) considered the syndrome to be a variant of GBS because of weakness and sensory changes in the limbs, absent deep tendon reflexes, and raised protein in CSF. However, he admitted that the signs were difficult to explain on a purely peripheral basis, because of the remarkable symmetry of the ophthalmologic manifestations during progression and recovery. Others believe that this syndrome involves both the central and the peripheral nervous system (3,4). The presence of bilateral ptosis as the only ophthalmologic finding does not resolve the issue of lesion location, the cause being either a central dorsal nuclear lesion of the oculomotor complex or lesions of both nerves innervating the levator palpebrae muscles.

Najim al-Din et al. (3) have shown that the ophthalmologic manifestations of the Fisher variant of GBS can vary greatly. Our patient confirms that they can also be minimal.

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Papilledema and Visual Loss as the Presenting Signs of a Primary Spinal Primitive Neuroectodermal Tumor

We report a patient with a primary spinal primitive neuroectodermal tumor (PNET) who presented with papilledema and visual loss before the appearance of myelopathic symptoms.

A 28-year-old woman had a 5-month history of intense headaches and progressive visual loss that affected her left eye more than her right eye. Best-corrected visual acuities were 20/50 in the right eye and 20/400 in the left eye. She was able to identify 11/11 Ishihara color plates with the right eye and 0/11 with the left eye. A relative afferent pupillary defect was noted in the left eye. Ophthalmoscopy revealed severe bilateral optic disc swelling associated with macular edema, retinal hemorrhages, and hard exudates (Fig. 1). Automated visual fields demonstrated severe constriction. Results of the neurological examination were normal.

Results of CT of the head and orbits and of brain MRI and magnetic resonance venography were normal. Lumbar puncture opening pressure was 630 mm H2O. There were 2 white blood cells (all mononuclear), 694 red blood cells, 500 mg/dL protein, and 16 mg/dL glucose. The elevated protein and decreased glucose levels raised concern for fungal or tuberculosis meningitis, although the patient did not have symptoms to suggest this diagnosis. Results of serum tests for syphilis, toxoplasmosis, HIV, hepatitis A, B, and C, tuberculosis, and Bartonella henselae were negative, as were results of cerebrospinal (CSF) fungal culture, India ink and KOH preparations, Gram stain, and acid fast bacilli (AFB) smear and culture.

The patient was treated with 250 mg methylprednisolone intravenously every 6 hours for 5 days and 500 mg acetazolamide intravenously every 6 hours for 5 days with no improvement in visual function. A left optic nerve sheath fenestration was performed with stabilization of vision.

Approximately 1 week after the optic nerve sheath fenestration was performed, the patient developed back pain and difficulty walking. Complete spine MRI showed 2 cervical intradural extramedullary masses at C3 and C7, 3 thoracic intramedullary enhancing masses at T4, T8, and
T12–L1, and 2 cauda equina masses, one at the left S1 root and the other in the posterior lumbar vertebrae at L2 (Fig. 2). Chest and abdominopelvic MRI showed no abnormalities. The patient refused further medical treatment. Two months later, she returned to the hospital complaining of decreased movement and sensation of both lower extremities and worsening of vision. She subsequently underwent optic nerve sheath fenestration on the right side. A T5–T7 laminectomy with intramedullary biopsy showed a primitive neuroectodermal tumor (PNET). She refused further intervention and died 3 months later of respiratory failure.

Papilledema associated with spinal cord tumors was first described by Taylor and Collier in 1901 (1). Since then the association of papilledema and spinal cord tumors has been well documented (2–12). However, papilledema and visual loss preceding myelopathic symptoms occurs much less frequently. There are 11 reported cases, including 1 in French and 1 in Spanish (13–19). In those patients, myelopathic signs developed between 1 and 7 months after the onset of visual symptoms. Five patients had hydrocephalus at presentation. All had elevated CSF protein with normal CSF glucose except for 1 patient with a low glucose level (19). The patient with the low CSF glucose level had a PNET but was treated for tuberculous meningitis before the correct diagnosis was made.

We emphasize not only that visual symptoms from papilledema may be a presenting feature of a spinal cord tumor before myelopathic manifestations have appeared but also that spinal fluid analysis may show elevated protein and decreased glucose levels and thus be mistaken for signs of infectious meningitis unless proper spinal imaging is done.

**REFERENCES**


The focus of the 2009 Association for Research in Vision and Ophthalmology (ARVO) annual meeting was “Reducing Disparities in Eye Disease and Treatment.” The keynote address was given by Hugh R. Taylor, MD, Melbourne, Australia, who discussed how huge disparities in eye health around the world are being addressed. The Proctor Medal was awarded to Joe G. Hollyfield, PhD, Cleveland Clinic Foundation, for his work in understanding the initiating events in age-related macular degeneration. The Weisenfeld Award went to Alan Bird, MD, FMedSci, University College London, for his seminal work on the biologic treatment of retinal disease. The Friedenwald Award winner was Samuel Miao-Sin Wu, PhD, Baylor College of Medicine, whose research has led to a better understanding of the synaptic organization of the vertebrate retina.

NEUROPROTECTION

Clinical trials of potential neuroprotective therapies in neurology and ophthalmology have had disappointing results despite potent neuroprotective effects in preclinical models (#298). Small differences in animal models or conditions used to induce neuronal injury can lead to large differences in outcome. It will probably be important to identify neuroprotective strategies that work in multiple models to increase chances of successful translation. Preclinical studies that focus on keeping retinal ganglion cells (RGCs) alive are also insufficient, as the remaining cells may not be functional. For example, RGCs in mice lacking Bax, a pro-apoptotic protein, do not die after optic nerve injury but do not function normally and develop suppressed gene expression due to histone deacetylation. Understanding such epigenetic factors that regulate gene expression may lead to novel therapeutic approaches to restore the function of surviving ganglion cells. Critical reevaluation of how to evaluate neuroprotection may lead to new therapeutic strategies for optic neuropathies and other neurodegenerative diseases.

Investigators reported promising neuroprotective effects for RGCs in models of glaucoma and traumatic optic nerve injury. For example, several groups showed neuroprotective effects of specific neurotrophic factors and are developing methods for stable long-term delivery. Mesenchymal stem cells (MSCs) from adult bone marrow that are engineered to express brain-derived growth factor (BDNF), glial-derived growth factor (GDNF), or nerve growth factor (NGF) will integrate into the retina after intravitreal injection and reduce the level of RGC loss after optic nerve transection (#1673). Another group found that MSCs secreting BDNF or GDNF prevent RGCs from dying in a laser-induced rat model of glaucoma (#2754). BDNF delivery by an alternate method—transfection of an adenoviral vector expressing BDNF—showed similar neuroprotection of RGCs after nerve transection (#2757). Consistent with observed effects of BDNF treatment, endogenous up-regulation of BDNF was detected in rat eyes with experimental glaucoma induced by injection of hypertonic saline into episcleral veins (#2760). Phosphine-borane complexes (PB-1 and PB-2) previously shown to reduce RGC loss after nerve injury were evaluated further to understand how they may protect neurons. In vitro studies revealed that PB-1 and PB-2 reduce disulfides and are probably able to cross the blood-brain barrier, but they do not scavenge the damaging reactive oxygen species superoxide (#3189). PB-1 was able to reduce proteins isolated from a RGC cell line, suggesting that changes in sulfhydryl oxidation from drug treatment may promote neuronal survival (#3190).

An Optic Nerve Regeneration Symposium (#272) focused on factors that may move the technology of optic nerve regeneration from theory to practice. It is currently accepted that intrinsic properties of the optic nerve and its environment prevent regeneration. These factors include reactive gliotic scar formation, myelin inhibitory proteins, and macrophage-associated scar retraction. Many factors have been evaluated to encourage re-growth of the RGC axons. One promising factor seems to be Bcl-2. Neonatal mice overexpressing Bcl-2 have been shown to be capable of regeneration of the entire length of the optic nerve. Removal of phosphatase and tensin homolog and tuberous sclerosis complex 1, which down-regulate the rapamycin pathway, can lead to protein synthesis helpful in regeneration. Directed growth of damaged axons to the site of
injury seems to require EphB3 receptor tyrosine kinase, which does not, however, prevent aberrant growth patterns. Intravitreal placement of factors that may promote photoreceptor regeneration may be the next site of application. It remains to be determined how the complex retinotopic arrangement of RGC axons in the pre- and post-geniculate visual pathways will be re-established with optic nerve regeneration.

**ASSESSING STRUCTURE-FUNCTION RELATIONSHIPS**

Pattern electroretinogram (ERG) amplitude and retinal nerve fiber layer (RNFL) thickness were diminished in patients with temporal hemianopia due to chiasmal compression (#929). Swelling of the RNFL from papilledema due to intracranial hypertension (IIH) is better shown by optical coherence tomography (OCT) than by slit lamp polarimetry (SLP), whereas SLP may be more useful than OCT to demonstrate axonal dilatation (#932). RNFL swelling from papilledema was greatest in the superior and inferior quadrants on OCT. There was no correlation between change in RNFL thickness and change in mean deviation on automated perimetry.

Forty-seven adult patients with monocular amblyopia (anisometropia, strabismic, deprivation, or idiopathic) had evidence on pattern visual evoked potentials (VEPs) of delayed P100 latency (118.69 msec) and an increased P100 latency ratio of 1.18 compared with control subjects (P100 latency [103.63 msec] and P100 latency ratio [1.03]) (#4708). Pattern VEPs may be helpful in confirming amblyopia in adults.

The RNFL is commonly thickened compared with that in the fellow eye during acute optic neuritis (ON) even though clinically the optic disc may not appear edematous. One month after the acute episode, most of the RNFL thickening has diminished. Persistent RNFL thickening at 1 month was predictive of poor long-term prognosis for visual recovery with continued RNFL loss progressing over the following 6 months (#926). Visual loss in patients with multiple sclerosis (MS) may be present even in the absence of a history of ON. Reductions in low-contrast acuity are associated with RNFL thinning, suggesting that axonal loss may be a significant contributor to visual dysfunction in MS. The rate of chronic axonal loss observed in patients with MS was greater than that seen in healthy patients, regardless of a previous history of ON. Progressive axonal loss can be detected in the optic nerves of patients with MS. Ocular imaging technologies are useful tools to evaluate structural abnormalities in the RNFL and changes over time (#927, #928).

RNFL birefringence reduction and recovery were studied using GDx in patients with acute ON. The percent change in thickness was calculated for each sector and globally in 10 subjects with the fellow eye as a control. There was acute thickening of the RNFL across all sectors on OCT and subsequent thinning over 6 months. Birefringence fell at baseline and recovered over time. Baseline birefringence reduction did not correlate with the 6-month mean deviation on automated perimetry or the amount of RNFL loss on OCT. Most of the birefringence reduction seems to be due to intra-axonal swelling and extra-axonal edema and seems to be recoverable (#5664).

Twenty patients who had recovered from ON underwent multifocal VEP testing (#5348). Among the areas most commonly affected, the cecocentral and arcuate nerve fiber bundle regions were found to have abnormally prolonged latencies, which correlated with defects seen on standard automated perimetry.

The RNFL was longitudinally evaluated in 23 carriers of Leber hereditary optic neuropathy (LHON) over 4 years (#934). Forty-eight percent of carriers with subclinical disease showed RNFL loss that was greatest in the superior and inferior quadrants. Subclinical pattern VEP abnormalities with prolonged latencies in P100 and N135 were found in clinically unaffected LHON carriers (#5347).

Macular thickness and RNFL thickness were both significantly smaller in eyes with band atrophy of the optic nerve compared with healthy control eyes. The macular thickness parameters of the nasal nerve fiber layer were the most predictive for differentiating eyes with band atrophy from control eyes. Macular thickness may have greater potential than RNFL thickness for assessing structure-function relationships in chiasmal disease. Global and sectoral macular and RNFL thickness differed significantly between eyes with band atrophy and healthy control eyes. Correlations were stronger between visual field loss and quadrantic or hemianopic nasal macular thickness than between visual field sector loss and sectoral RNFL thickness. The strongest correlation was observed between macular thickness in the inferonasal quadrant and visual field sectoral loss in the superior-temporal central quadrant (#930).

Evaluation of Humphrey matrix frequency doubling technology (matrix FDT), a newer program that uses smaller spot size than original FDT perimeter, showed a high correlation to defects detected on standard Humphrey visual field (HVF) perimeter for pre-chiasmal and post-chiasmal visual field loss (#5352). Prior studies of the original FDT had shown poor correlation for post-chiasmal lesions. Rarebit perimetry, a newer technology that uses supra-threshold small spot sizes 1/100 the size of standard HVF testing, was evaluated for its possible role as a bedside test in the inpatient setting (#5353). Rarebit perimetry was performed using a laptop computer for 29 eyes with visual field loss to test subjects lying in a hospital bed. Each eye also had been tested with the HVF 24-2 SITA program.
OPTIC NERVE

A retrospective review of visual outcomes in patients with neuromyelitis optica treated with rituximab compared with those of patients treated with other, more conventional, immunosuppressive therapies suggested that vision may recover better with rituximab (#1439). However, only 3 rituximab-treated patients were reported, with all 3 returning to baseline vision within a 6-month to 2-year available follow-up period.

A study of optic nerves from 2 brothers affected by LHON showed that decreased optic nerve size seems to predispose to phenotypic expression of LHON and may also be responsible for a more severe level of visual and structural nerve degeneration (#5350). Analysis of the RNA transcription profile extracted from leukocytes from 4 men with the 11778 LHON mutation who had experienced visual loss many years earlier revealed 137 up-regulated genes and 152 down-regulated genes hypothesized to be involved in cellular transport and transcription. ND4 and other mitochondria-encoded genes were not differentially expressed. The OPA1 gene was down-regulated in each of the 4 patients (#3468).

Axonal mitochondrial DNA copy number was found to be correlated with the pattern of axonal degeneration in histologic analysis of optic nerves from 4 patients with LHON (#3469). A retrospective review of 7 patients with LHON who were treated with idebenone (360–540 mg/day for 2 months to 1.5 years), a synthetic analog of coenzyme Q, revealed that 3 patients had significant improvement in visual acuity, visual fields, and color vision (#1440). Two patients who improved had the 11778 mutation; 1 patient had the 14484 mutation. Stimulation of ATP production by idebenone or other mechanisms may be useful for treating LHON. Related results in a rodent glaucoma model demonstrated that topical coenzyme Q10 administration reduces retinal ganglion cell loss through increased expression of cyclinophil D and cytochrome c oxidase (#4046), suggesting that coenzyme Q may have benefits for a variety of optic nerve stressors. Studies in a mouse model of LHON demonstrated long-term protection of RGCs and stable expression of ND4 in an AAV2 vector (#1443). Targeted gene therapy to replace mutant mitochondrial gene products through chromosomal DNA with a mitochondrial localizing sequence presents another potential strategy for long-term preservation of RGCs in LHON.

A study of 4 eyes from 2 Brazilian men with LHON who had the 11778 mutation and 4 age-matched control subjects demonstrated that melanopsin-containing RGCs are partially spared by neurodegeneration in LHON (#2559). Melanopsin-containing RGCs seems to withstand the degeneration process, consistent with the preservation of the pupillary light reflex and circadian rhythm seen in patients with LHON. Light-induced melatonin suppression after exposure to monochromatic blue light was unaffected in 5 patients with LHON and in 4 patients with dominant optic atrophy compared with control subjects (#5663).

245-Hydroxycholesterol, a by-product of enzymatic oxidation of cholesterol in neurons, seems to be a biomarker of some optic neuropathies. Retinal and plasma levels were measured using gas chromatography and mass spectrometry in an animal model for optic nerve disease. Plasma levels were also monitored in patients with ischemic optic neuropathy (ION) 1 day–6 months after onset of visual loss. Plasma levels increased 3-fold in the animal model. Patients with ION showed increased levels compared with those in age-matched control subjects (#3200).

In a novel rat model for ION, erythrosin B dye was activated with a YAG laser at 532 nm for 90 seconds at 200 mV to photochemically induce an ischemic injury 3 mm posterior to the optic disc. There was 50% RGC survival at 4 weeks (#3198). This paradigm seems to be a good model for posterior ION. Using the photochemical thrombosis mouse model for anterior ION, αB crystallin, a heat shock protein, was up-regulated (#3463). Exogenously delivered αB crystallin did not increase RGC survival and improved latency but not amplitude in the flash VEP.

In a prospective study of 304 asymptomatic morbidly obese patients, screening with nonmydriatic fundus photography for optic disc edema identified only 1 patient (#4020), suggesting that screening for asymptomatic IIH is not cost-effective in this population. The sensitivity and specificity of ultrasound to detect intracranial nerve sheath fluid for distinguishing papilledema from pseudopapilledema in patients with elevated optic disc pressure was examined in a retrospective review of 44 patients (#4021). Twenty patients had true papilledema, confirmed by elevated opening pressure on lumbar puncture, and 24 had pseudopapilledema. Among the 20 patients with papilledema, 19 (95%) had positive fluid signs on ultrasound. Among the 24 patients with pseudopapilledema, 10 (40%) had positive fluid signs on ultrasound. These results suggest that a negative ultrasound fluid test may be...
useful to exclude papilledema but that a positive test may falsely suggest papilledema quite often.

The ability of a portable home-monitoring device to detect whether patients with nonarteritic anterior ION (NAION) have obstructive sleep apnea (OSA) was examined (#4023). Of 15 patients monitored, 5 (33%) were found to have OSA, consistent with published reports that OSA incidence is increased in patients with NAION. Further development of this device may lead to easier and cheaper evaluation for patients by reducing the need for traditional sleep studies.

Histologic evaluation of optic nerves from patients with Alzheimer disease (AD) detected the presence of S-100 A12 (calgranulin C) (#4027). The staining pattern showed a plaque-like structure similar to plaques seen in brain lesions, suggesting that S-100 A12 plaques can form in optic nerves and may contribute to disease pathology. Further studies by this group identified additional potential pathogenic markers of AD-related optic neuropathy, including the receptor for advanced glycation end products. Detected in microvascular endothelial cells of optic nerves from patients with AD, they are known to bind a variety of ligands, including β-amyloid (#5345). High-mobility group box 1, a nonhistone DNA binding protein, was found by immunohistochemical analysis in the extracellular matrix of 12 optic nerves from patients with AD but not in the optic nerves of control subjects (#5351). Whether these proteins play a causative or bystander role is still unknown.

Nuclear magnetic resonance-based metabolomic analysis, used to detect metabolites including proteins, amino acids, drug compounds, and lipids, was used to screen blood and spinal fluid samples from patients with a variety of central nervous system (CNS) diseases (#4036). Results showed that reproducible disease-specific patterns could be identified. The metabolomic analysis pattern in 21 patients with IHH was 80% sensitive and 80% specific in distinguishing this condition from a full spectrum of CNS diseases, and analysis patterns in 17 patients with MS were also 80% sensitive and specific. Further refinement is needed, but results suggest that this technology will be useful for identifying biomarkers to aid in diagnosis and monitoring of disease.

Long-term follow-up of patients who underwent optic nerve sheath fenestration suggested that early intervention may be useful to better preserve vision (#1441). A retrospective review showed that 88% of patients with 20/40 or better visual acuity at the time of surgery retained 20/40 or better after surgery. Of patients with 20/50–20/200 visual acuity, 34% improved to 20/40 or better postoperatively, whereas only 9% of patients with visual acuity poorer than 20/200 vision improved to 20/40 or better and only 5% improved to 20/50–20/200. Investigators are using an infrared laser to perform endoscopic optic nerve sheath fenestrations (#1442) in an attempt to reduce surgical complications.

**ORBIT**

Upper eyelid injection of triamcinolone (40 mg) to treat lid retraction and orbital swelling (#650) in patients with thyroid-related orbitopathy was evaluated. Average palpebral height decreased from 9.6 to 8.7 mm in 20 eyes, and 19 of 22 eyes showed improvement in orbital swelling. The only complication was a mild elevation in intraocular pressure in 1 patient.

Axial globe position seems to have an effect on eyelid excursion (#656). In 58 patients, every 1-mm decrease in axial globe position measured by exophthalmometry resulted in a 0.4-mm decrease in levator function, which should be kept in mind when one is evaluating patients for neuromuscular disease.

No correlations were found between MRI volumetric analysis of extraocular muscle (EOM) motility and diplopia as measured by plotting the zone of single binocular vision on Goldmann perimetry (#1981).

A retrospective review of long-term (>4 year) follow-up data of patients with ocular myasthenia gravis confirmed results of earlier shorter-term studies showing that patients treated with prednisone were less likely to develop generalized disease (GMG) and less likely to have diplopia than patients who did not receive prednisone (#1436). Of 87 patients, 55 were treated with prednisone, with 13% developing GMG and 27% having diplopia at the last recorded visit (mean = 7.2 years). In comparison, 50% of the 32 patients not treated with prednisone developed GMG, and 57% had diplopia at the last follow-up (4.6 years).

In a review of 176 temporal artery biopsies, older age and higher sedimentation rate were correlated with greater likelihood of positive biopsy results in patients. Although women were more likely to undergo biopsy, the likelihood of positive biopsy results was not significantly different from that in men. Longer biopsy specimens were not associated with a higher likelihood of positive pathology. The choice of surgical service to perform the biopsy did not seem to have any correlation to the results of the biopsy (#4017).

Lay observers were evaluated for their ability to detect strabismus in subjects from various ethnic groups in 12 digitally simulated esotropia and exotropia models (#1993). With 70% as a positive detection rate, the critical magnitude was 18.82 prism-diopeters (PD) for esotropia (ET) and 16.63 PD for exotropia (XT). ET was easier to detect than XT among Asians and the opposite was true for Caucasians and African Americans.

Eight subjects performed voluntary and “visually guided saccades” while undergoing 3-T functional MRI (#2879). The superior parietal cortex and the dorsolateral prefrontal cortex seemed to be most involved in vertical saccades.
Caffeine increased ocular microtremor and micro-saccades within 30 minutes in 20 healthy subjects given 180 mg of regular coffee but not in subjects given decaffeinated coffee (#2882). Autopsied EOMs of patients with amyotrophic lateral sclerosis (ALS) were compared with autopsied control EOMs in a mice model of ALS (#3038). Decreased expression of gangliosides GD1b and GQ1b/GT1a and Schwann cell marker S-100 were noted in patients with ALS. Parvalbumin, believed to be protective for EOMs in patients with early ALS, was diminished in these patients with end-stage ALS. Both patients with ALS and transgenic ALS mice with the D90A mutation had similar changes in the extracellular matrix of EOMs that may make the mouse model useful in evaluating progressive changes in EOMs.

**VISUAL PATHWAY**

Eight-three patients have been enrolled in a community-based, multicenter trial evaluating the potential benefit of high-power (57 PD) peripheral prism glasses for homonymous hemianopia (#3210). Peripheral Fresnel prism segments were fitted unilaterally on the side of the field loss. Preliminary results showed that 68% of patients believed that the high-power peripheral prism helped in obstacle avoidance. In another study (#4734), hemianopic patients were evaluated for scotomas in visual space located at the prism apex with either 40- or 57-PD base out Fresnel prisms. One of 4 patients with 57 PD had binocular (10° lateral extent) scotomas. These scotomas are important to recognize in future designs of bilateral prism glasses for hemianopic field expansion.

The ability to drive a 14-mile route in an automobile was tested in 30 patients with homonymous hemianopia or quadrantanopia and 30 matched control subjects with normal visual fields 6 months after brain injury (#3204). Patients with visual field defects were likely to drive more slowly and accelerate less often. These driving characteristics are different from those seen in unsafe drivers.

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The scientific sessions this year included 2021 platform presentations and posters. There were 11 educational courses in neuro-ophthalmology and neuro-otology given by the following faculty: Robert Baloh, Laura Balcer, Valerie Biousse, James Corbett, Wayne Cornblath, Fiona Costello, Kathleen Digre, Eric Eggenberger, Scott Eggers, Terry Fife, Steven Galetta, Christopher Glisson, James Hain, Janet Helmsinski, Aki Kawasaki, David Kumpe, Nancy Newman, David Newman-Toker, Victoria Pelak, Sharon Polensek, Valerie Purvin, John Pula, Janet Rucker, Jonathan Trobe, Ronald Tusa, Grant Liu, Mark Moster, Nancy Newman, David Newman-Toker, Victoria Pelak, Sharon Polensek, Valerie Purvin, John Pula, Janet Rucker, Jonathan Trobe, Ronald Tusa, Gregory Van Stavern, and David Zee. The topics most relevant to neuro-ophthalmologists are summarized here.

NEURODEGENERATIVE DISEASES

Adam Boxer and colleagues (San Francisco, CA) used eye movement recordings to identify clinical differences in patients with frontotemporal lobar degeneration (FTLD) who had tau vs. TDP-43 autopsy pathology. The investigators recorded saccades in 11 patients with FTLD-TDP-43 and 10 patients with FTLD-tau. Horizontal and vertical saccade times were higher in the tau group than the TDP-43 group ($P < 0.02$). Using a receiver operating curve (ROC) analysis, the authors demonstrated that slowed saccades accurately distinguished TDP-43 from tau patients. Detailed examination of the brainstem ocular motor nuclei was conducted in 5 representative patients and revealed increased pathologic burden in the tau patients. The authors concluded that saccadic abnormalities are a useful predictor of pathologic subtypes of FTLD, possibly due to greater brainstem involvement in the tau subtype. (S42.006)

Shawn Smyth and colleagues (Aurora, CO) conducted a retrospective study of computerized visual field (CVF) defects in 9 patients with clinically diagnosed posterior cortical atrophy (PCA). Ten patients and 10 control subjects were studied at presentation, after 1 month, and after 4 months with visual acuity, computerized visual fields, contrast sensitivity, color perception, static high-contrast object detection, motion detection, coherent moving noise perception, and object-from-motion (OFM) perception. One month after the acute phase, the initial deficits of visual acuity, contrast sensitivity, color perception, visual fields, and static object detection had returned to normal or near-normal levels in 9 of 10 patients. However, the patients had persistently defective motion processing, with reduced OFM perception, higher motion detection thresholds, and prolonged reaction times. The level of OFM impairment correlated with the conduction delay detected on visual evoked potentials. The authors suggested that abnormalities of the magnocellular pathway after ON may be responsible for the patients’ persistent visual complaints, particularly regarding motion processing, despite normal standard visual testing. Low-contrast acuity, which is probably mediated by the parvocellular pathway, was not assessed. (P09.171)

OPTIC NEURITIS AND MULTIPLE SCLEROSIS

Noa Raz and colleagues (Jerusalem, Israel) conducted psychophysical tests of visual function in patients with acute optic neuritis (ON) to characterize the deficits with respect to parvocellular and magnocellular pathways. Ten patients and 10 control subjects were studied at presentation, after 1 month, and after 4 months with visual acuity, computerized visual fields, contrast sensitivity, color perception, static high-contrast object detection, motion detection, coherent moving noise perception, and object-from-motion (OFM) perception. One month after the acute phase, the initial deficits of visual acuity, contrast sensitivity, color perception, visual fields, and static object detection had returned to normal or near-normal levels in 9 of 10 patients. However, the patients had persistently defective motion processing, with reduced OFM perception, higher motion detection thresholds, and prolonged reaction times. The level of OFM impairment correlated with the conduction delay detected on visual evoked potentials. The authors suggested that abnormalities of the magnocellular pathway after ON may be responsible for the patients’ persistent visual complaints, particularly regarding motion processing, despite normal standard visual testing. Low-contrast acuity, which is probably mediated by the parvocellular pathway, was not assessed. (P04.077)

Takafumi Hosokawa and colleagues (Osaka, Japan) reported a retrospective analysis of Goldmann visual field defects after ON in 15 patients with neuromyelitis optica (NMO) and 20 patients with multiple sclerosis (MS). Anti-aquaporin 4 antibodies were positive in all patients with NMO and negative in all patients with MS ($P < 0.05$). The authors suggested that an altitudinal field defect may distinguish NMO from MS and postulated an ischemic mechanism for the optic neuropathy in NMO. The study was limited by a small
patients with ON had altitudinal defects. (P04.093)

Claire Riley and colleagues (New York, NY) conducted a meta-analysis to evaluate the prognostic value of cerebrospinal fluid (CSF) abnormalities in patients with a clinically isolated syndrome (CIS) and >2 MRI lesions to determine progression to clinically definite multiple sclerosis (cdMS). Using unpublished data from the trials of glatiramer acetate and interferon beta for patients with CIS (BENEFIT, IFNβ-1a ETOMS, and GA PreCISE), they examined the CSF results and clinical outcomes from patients receiving placebo. Abnormal CSF was defined as oligoclonal banding (OCBs) and/or an elevated IgG index, and patients without both sets of these data were excluded. The presence of a CSF abnormality did not predict the likelihood of progression to cdMS. In addition, this study demonstrated that most patients with CIS and MRI abnormalities also have CSF abnormalities, but that the presence of CSF abnormalities does not have significant additional prognostic value in predicting the risk of cdMS over 2 years. (P02.119)

Jonathan McNulty and colleagues (Dublin, Ireland) conducted a diffusion tensor tractography study to evaluate the integrity of the medial longitudinal fasciculus (MLF) in patients with internuclear ophthalmoplegia (INO). They studied 12 patients with INO and 12 matched control subjects. Participants underwent conventional MRI and diffusion tensor imaging. Regions of interest approximating the MLF were identified. Qualitative MLF abnormalities were detected in all 12 subjects and in no control subjects. Oneshortcoming was that this method is not specific and produces extraneous fiber tracts apart from the MLF. (P04.082)

Ari Green and colleagues (San Francisco, CA) reported the correlation between N-acetylaspartate (NAA) levels in normal-appearing gray matter (NAGM) and a measurement of retinal nerve fiber layer (RNFL) thickness performed 2 years later in a cohort of patients with MS and CIS. They studied 179 patients (aged 32.9 ± 9.5, 65% women) using proton spectroscopy imaging (1H-magnetic resonance spectroscopy [MRS]). NAGM NAA values correlated with average RNFL measures ($R = 0.22, P < 0.0001$). This study demonstrates that reduced cerebral NAA levels are predictive of future axonal loss in the anterior visual pathway. (P05.156)

Esther Bisker and colleagues (Philadelphia, PA) conducted a longitudinal study to assess the degree of RNFL thinning associated with the loss of low-contrast acuity and high-contrast acuity in patients with MS. In their study, 365 patients (725 eyes) underwent optical coherence tomography (OCT)-3 imaging at baseline and at 6-month intervals during a mean follow-up period of 1.5 years (range 0.5-3.7 years) at three academic centers. Visual function testing was performed using low-contrast (2.5 and 1.25% levels) and Early Treatment Diabetic Retinopathy Study (ETDRS) acuity charts. Worsening of low-contrast acuity was noted in 33% of MS eyes. Of these eyes with visual loss, only one third had a known history of ON. Two-line (10-letter) losses of 2.5% low-contrast acuity were associated with a 1.6-μm decrement in RNFL thickness over time ($P = 0.009$), and losses of 1.25% contrast acuity were associated with a 3.7-μm decrement ($P = 0.02$). The authors concluded that visual loss may be present even in the absence of a history of ON and that reduced low-contrast acuity is associated with RNFL thinning over time. These findings suggest that gradual optic nerve axonal loss may be an important feature of MS. (S57.004)

Deanna Cettomai and colleagues (Baltimore, MD) reported the concordance between RNFL thickness measured by OCT and the clinical findings of optic nerve pallor or afferent pupillary defect (APD) on 212 consecutive patients. The mean RNFL was 96 ± 15 m (n = 366) in eyes without pallor and 78.7 ± 20.6 m (n = 58) in eyes with pallor. Mean RNFL was 84.7 ± 16.1 m (n = 41) for eyes with an APD was detected and 95.4 ± 16.8 μm (n = 383) for eyes without an APD. In patients for whom the ratio of the mean RNFL between the two eyes was <90%, an APD was detected on clinical examination in 86% (sensitivity = 0.28, specificity = 0.93). There was wide variability across physicians in the accuracy of detecting pallor or an APD. The authors suggested that OCT is a more sensitive measure of subclinical optic nerve damage than clinical examination alone and that OCT may be a useful adjunct in the management of patients with MS. (P05.158)

Salim Abboud and colleagues (Hinckley, OH) reported their findings on the reproducibility of serial OCT without pharmacologic pupillary dilation (PPD). They conducted 2 serial measurements at least 1 week apart of the peripapillary RNFL thickness and macular volume (MV) in 10 consecutive healthy volunteers by Stratus OCT without PPD. All studies were conducted by a single operator. Across subjects, the coefficient of variation (COV) for independent serial measures of RNFL was 2.86% and for MV was 1.90%. The authors concluded that serial measurements of RNFL and MV are sufficiently precise to use as outcome measures in longitudinal studies, even when implemented without PPD. (P05.164)

Sally Chang and colleagues (Philadelphia, PA) evaluated the utility of measuring low-contrast acuity in addition to the standard Multiple Sclerosis Functional Composite (MSFC) by assessing the strength of correlations of these assessments with RNFL thickness measurements. They studied 164 patients (326 eyes, aged 47 ± 10 years), measuring low-contrast letter acuity (2.5% and 1.25% levels), high-contrast acuity (ETDRS charts), and
standard MSFC. Scores for MSFC with low-contrast acuity added (MSFC-4) had greater correlations with RNFL thickness compared with the standard MSFC ($P = 0.07$ for MSFC, $P = 0.005$ for MSFC-4 with $2.5\%$ low-contrast, and $P = 0.007$ for MSFC-4 with $1.25\%$ contrast). The authors concluded that measurement of low-contrast acuity increases the capacity of the MSFC to capture the effects of axonal loss in the anterior visual pathway. (P04.076)

Guradesh Bedi and colleagues (Miami Beach, FL) conducted a retrospective study to evaluate the efficacy of rituximab on the relapse rate and disability in NMO. Among 19 patients treated with rituximab, relapses occurred in 5 patients. The authors concluded that rituximab leads to a significant reduction in relapses in patients with NMO. (P04.099)

**NONARTERITIC ANTERIOR ISCHEMIC OPTIC NEUROPATHY**

Edward Atkins and colleagues (Atlanta, GA) evaluated the treatment of nonarteritic anterior ischemic optic neuropathy (NAION) in the United States using a Web-based anonymous survey ($n = 1595$) of US neuro-ophthalmologists (US-NO = 350), Georgia ophthalmologists (GA-O = 340), Georgia neurologists (GA-N = 322), and Georgia optometrists (GA-OD = 583). For acute treatment, 63% of GA-N and GA-O and 80% of US-NO use antiplatelet agents, 10% of physicians use oral steroids, 19% of GA-N use high-dose intravenous steroids, 22% of US-NO and 13% of GA-O use topical brimonidine, and 7% of US-NO use intravitreal bevacizumab. For secondary prevention of fellow eye involvement, >74% physicians use antiplatelet agents, whereas 10%-15% of ophthalmology-trained US-NO and GA-O also use brimonidine in this setting. More than 80% of physicians manage vascular risk factors aggressively; 15% of US-NO obtain carotid ultrasound compared with 51% of GA-O and 72% of GA-N, and 16% of US-NO obtain neuro-imaging compared with 25% of GA-O and 84% of GA-N. The authors conclude that, despite insufficient evidence, most physicians currently use antiplatelet agents for acute treatment and secondary prevention of NAION. Other popular treatments include intravitreal bevacizumab, topical brimonidine, and steroids. Neurologists are less familiar with the management of NAION than ophthalmologists and neuro-ophthalmologists. (P04.079)

**VISUAL LOSS**

Wolfgang Heide and colleagues (Celle, Germany) investigated visual search patterns in patients with acute HH. They tested the hypothesis that visual search in HH is determined purely by the visual-sensory deficit by comparing 9 patients with HH due to acute occipital stroke with 9 healthy subjects with a simulated “virtual” HH (VHH) and 9 control subjects with normal visual fields. They recorded eye movements while subjects searched for targets among distractors. All patients, even those with small lesions restricted to the visual cortex, showed longer search durations than VHH subjects. Their longer search duration correlated with a higher number of both fixations and “re-fixations” (repeated scanning of fixated items). Scan-path strategies were similar in HH and VHH subjects. The authors concluded that pure visual input failure alone does not fully account for abnormal visual search in patients with isolated occipital lesions. They postulate that the longer search durations may result either from changes in visual attention due to disconnections of the visual cortex or from an early stage of compensatory eye movements. (S57.005)

Sashank Prasad (Philadelphia, PA) received the S. Weir Mitchell award for excellence in basic science research from the American Academy of Neurology Alliance. He and his colleagues studied structural and functional changes of the visual pathway in patients with early-onset blindness. They studied 10 blind subjects and 10 sighted control subjects, collecting BOLD functional MRI (fMRI) data (during a language comprehension/semantic decision task), a volumetric anatomical scan, a resting perfusion scan, and diffusion tensor imaging. They found that during sentence comprehension, blind subjects demonstrated significant occipital activation in addition to left hemispheric language areas (BOLD $\Delta$, blind 0.9% vs. sighted 0.0%; $P < 0.05$). Furthermore, they found a positive correlation across subjects between resting occipital perfusion and the amount of cross-modal task activation ($R = 0.5$; $P < 0.05$). In addition, white matter atrophy and a reduction in anisotropy were correlated ($R = 0.7$; $P = 0.07$). On the other hand, no structural measures predicted the amount of functional cross-modal activation ($P > 0.1$). The authors concluded that significant structural and functional differences exist between early-blind and sighted subjects. In addition, lack of correlation between structural and functional measures may suggest that these forms of plasticity are independent in the brain’s response to early blindness. A larger study is necessary to explore that possibility.

**IDIOPATHIC INTRACRANIAL HYPERTENSION**

In a retrospective review of 230 consecutive patients with idiopathic intracranial hypertension (IIH) over 8 years, Sachin Kedar and colleagues (Jackson, MS) studied the effect of patient factors on the level of opening pressure (OP) in patients at presentation and the effect of OP on visual outcomes. They found an OP at presentation of $388 \pm 93$ mm H$_2$O that negatively correlated with age ($r = 0.2$). Gender, race, initial body mass index (BMI), weight
change, presenting symptom, and time interval to presentation were not associated with OP. Higher OP was associated with worse initial vision. Patients with visual acuity (VAS) ≥20/100 had an OP of 382 ± 90 mm H2O and those with a VAS <20/100 had an OP of 515 ± 77 mm H2O; patients with normal visual fields (VF) had an OP of 390 ± 85 mm H2O and those with severely constricted VF s had an OP of 439 ± 110 mm H2O. Patients with normal-appearing optic nerves had an OP of 358 ± 94 mm H2O, whereas those with grade 4–5 papilledema had an OP of 439 ± 109 mm H2O. There was no significant association, however, between OP and visual outcome (improvement or worsening of VA or VFs or appearance of ON during follow-up). The authors concluded that a higher presenting OP in patients with IIH is associated with worse initial VA, VF loss, and ON appearance, but that OP is not predictive of the clinical course. (P04.080)

J. Alexander Fraser and colleagues (Atlanta, GA) conducted a case-control study to evaluate potential risk factors for IIH in 24 men and matched control subjects. They administered a telephone questionnaire (including the Androgen Deficiency of Aging Men [ADAM] questionnaire for hypogonadism and the Berlin questionnaire for sleep apnea) and explored medical comorbidities, obesity patterns, endocrinologic problems, reproductive health, medications and drugs, and sleep apnea. After controlling for BMI, men with IIH were more likely than control subjects to have symptoms of androgen insufficiency. The authors concluded that men with IIH have a higher prevalence of symptoms suggestive of androgen deficiency and sleep apnea and that these factors may be etiologically related. (P04.071)

Beau Bruce and colleagues (Decatur, GA) conducted a retrospective cohort study of 411 consecutive adults with IIH and 38 matched control subjects from three centers. In this group they identified 20 patients (5%) older than 50 years at diagnosis and 18 (4%) with a normal BMI. Both groups were more likely to be white (P = 0.04, 75% vs. 49%) than the rest of the IIH cohort. Older patients with IIH had a lower BMI but were still generally obese (P = 0.025, 33% vs. 38%). At presentation, they were less likely to report headache (P < 0.001, 35% vs. 76%) and more likely to complain of visual changes (P = 0.01, 45% vs. 21%). At last follow-up, they were more likely to have persistent optic disc edema (P = 0.002), but they had similar, if not better, visual outcomes than younger patients did. Among patients with normal BMI, medication-induced IIH was more frequent (P = 0.007, 28% vs. 7%). No patient with IIH who had a normal BMI had severe visual loss in either eye (P = 0.09, 0% vs. 16%). The authors concluded that older patients and those with a normal BMI make up a small proportion of those with IIH but seem to have better visual outcomes than typical patients with IIH. (P04.072)

HEREDITARY DISEASES

Margherita Milone and colleagues (Rochester, MN) reported a patient with progressive external ophthalmoplegia and a mutation in OPA1 without associated visual loss or optic atrophy. The patient was a 48-year-old woman who had myopathy, neurosensory hearing loss, migraine, and gastrointestinal dysmotility in addition to ophthalmoplegia. There was no loss of visual acuity, optic atrophy, visual field defect, or dyschromatopsia, although neither optical coherence tomography nor visual evoked potentials were performed. Electromyography revealed myopathy and muscle biopsy revealed cytochrome c oxidase (COX)-negative fibers (but not ragged-red fibers). Multiple mitochondrial DNA (mtDNA) mutations were identified. The autosomal genes commonly associated with multiple mtDNA deletions (POLG1, POLG2, ANT1, and PE O1) were sequenced, and no mutations were found. A heterozygous in-frame deletion (p.R38 S43del) was identified in OPA1, which has been reported previously in two Danish patients with nonsyndromic autosomal dominant optic atrophy. The case broadens the spectrum of phenotypes associated with OPA1 mutations by demonstrating multiple systemic abnormalities in the absence of optic nerve dysfunction. (P01.050)

Gerald Pfeffer and colleagues (Vancouver, BC) conducted a retrospective study of patients with chronic progressive external ophthalmoplegia (CPEO) to compare the yield of levator palpebrae biopsy to skeletal muscle biopsy. In a chart review of 36 patients with CPEO who underwent biopsy and had mitochondrial DNA testing, they found that the diagnostic yield of a skeletal biopsy was 50% (13 of 26) and that of a levator palpebrae biopsy was 85% (11 of 13). Three of the subjects who initially had negative skeletal muscle biopsies subsequently had positive levator palpebrae biopsies. The authors suggested that patients with CPEO undergoing levator palpebrae resection should undergo a biopsy of that muscle because of its higher yield. (S55.005)

Valeria Barcella and colleagues (Milan, Italy) reported abnormalities of the pregeniculate and postgeniculate visual pathway in patients with LHON studied by MRI. They studied 5 patients with LHON and 10 healthy control subjects. They assessed the correlations between diffusion tensor (DT) tractography and voxel-based morphometry (VBM) data with OCT measures and fMRI activity of the visual cortex. VBM analyses revealed optic nerve and chiasm atrophy, as well as a significant reduction of occipital gray matter, in all patients with LHON. There was reduced fractional anisotropy (FA) in the left optic radiation, which correlated across subjects with OCT RNFL measurements. The patients demonstrated reduced activation in area VI bilaterally. The authors concluded that optic nerve damage in LHON may induce retrograde
structural and functional changes of the visual pathways, although the study does not exclude the possibility that retrogenticulate alterations are also directly due to mitochondrial dysfunction. (S57.003)

Matthew Kirkman and colleagues (Newcastle upon Tyne, UK) assessed visual disability in the role of environmental DNA mutation G3460A [n = 71], G11778A [n = 270], and T14484C [n = 61], identified from 125 independent pedigrees. Of these, 196 were clinically affected, and 74.5% of the affected subjects were men. Subjects received a structured questionnaire focusing on alcohol and tobacco exposure (before visual loss for affected individuals), and the Visual Function Index (VF-14) scale, which assesses impairment in activities of daily living, ranging from 0 (worst) to 100 (best). Affected patients with the T14484C mutation had higher VF-14 scores compared with those with the G3460A and G11778A mutations (P < 0.0001). Heavy cumulative tobacco consumption was significantly associated with visual loss in a binary logistic regression model (odds ratio [OR] 3.26, 95% confidence interval [CI] 1.31–8.07, P = 0.011). Maximum intensity of alcohol consumption, on the other hand, did not correlate with visual loss on multivariate analysis (OR 2.75, 95% CI 0.76–10.02, P = 0.125). The authors concluded that the VF-14 provides a useful tool in assessing visual dysfunction in LHON and that smoking may contribute to reduced visual function. The role of alcohol consumption is not so clear. (IN2-1.004)

Valerio Carelli and colleagues (Bologna, Italy) reported a correlation in LHON between axonal mtDNA copy number and the pattern of neurodegeneration in optic nerve cross sections. Their conclusions were based on a post-mortem analysis of 2 LHON/11778 patients (4 eyes) and 6 control subjects (12 eyes). They found that the mtDNA content/central regions of the optic nerve was significantly lower (P < 0.05) than in the superior, nasal, and inferior regions. They concluded that the papillomacular bundle axons of the temporal quadrant are the most vulnerable in LHON and have the lowest amount of mtDNA. The mechanism by which reduced mtDNA copy number and ganglion cell death are linked remains to be elucidated. (P04.073)

Chiara La Morgia and colleagues (Bologna, Italy) assessed the integrity of the retinohypothalamic tract (RHT) that originates from the intrinsically photosensitive melanopsin-containing retinal ganglion cells (ipRGCs) in mitochondrial optic neuropathies. They studied 5 patients with LHON, 4 patients with dominant optic atrophy, and 9 control subjects. They assessed optic neuropathy severity by OCT. A melatonin suppression test (MST) was performed, collecting plasma samples hourly from 12:30 pm to 3:30 am and performing a nighttime suppression test using monochromatic (470 nm) blue light between 1:30 and 3:30 am. The suppression score was calculated by comparing the suppression night melatonin level to the baseline night level. A significant suppression of melatonin plasma levels by light was observed in control subjects (67 ± 17%) and in patients (LHON 65 ± 25%; DOA 57 ± 33%) without a difference between groups. From post-mortem eyes of 2 patients with LHON and 2 control subjects, immunohistochemical analysis of retinal sections through the optic nerve head revealed a relative preservation of ipRGCs in patients with LHON compared with control subjects, despite the severe loss of total RGCs. The authors concluded that in LHON and DOA, there is preservation of circadian phototransduction. Their autopsy study in LHON suggests that this may relate to sparing of ipRGCs. (IN5-2.00)

NEUROMUSCULAR DISEASE

Mark Kupersmith (New York, NY) conducted a retrospective analysis of patients with ocular myasthenia gravis (OMG) to determine the effect of chronic low-dose corticosteroids in controlling diplopia and preventing progression to generalized myasthenia gravis (GMG). Patients who had OMG for longer than 4 years or who subsequently developed GMG were identified. Unless contraindicated, patients with diplopia generally received prednisone therapy. Diplopia was present at the last examination in 27% of the prednisone-treated group and 57% of the prednisone-untreated group. Although the study is limited by its retrospective design, the authors concluded that in patients with OMG, prednisone may reduce the incidence of GMG, delay its onset, and control diplopia. (S55.002)

Michael Hehir and colleagues (Charlottesville, VA) retrospectively evaluated the outcomes of a large cohort of patients with GMG treated with mycophenolate mofetil (MMF). Two recent randomized controlled trials (RCTs) have failed to demonstrate benefit of MMF over prednisone alone as initial immunotherapy, but these studies were limited by short duration or sensitive outcome measures. The authors reviewed the clinical outcomes of seropositive patients with myasthenia gravis receiving MMF monotherapy (n = 35) or MMF + prednisone therapy (n = 68) for longer than 3 months. Patients were assessed by MG- Manual Muscle Test (MMT) score and MGFA Post-Intervention Status (PIS). Median follow-up was 2.2 years; 60% were followed ≥24 months. Patients treated with MMF monotherapy began to improve between 6 and 12 months; 80% of patients followed for ≥24 months had an MMT <4 and PIS of minimal manifestations or pharmacologic remission. Patients treated with combination therapy had a prednisone dose reduction after 12 months; at ≥24 months, 53% had been weaned completely from
prednisone and 75% took <7.5 mg prednisone/day. Three patients discontinued MMF because of side effects. The authors concluded that MMF is an effective treatment as either monotherapy or adjunctive therapy to prednisone. The long follow-up demonstrated a corticosteroid-sparing effect of MMF during the second and third year of therapy that could not be demonstrated by studies of shorter duration. This study, however, did not include patients treated with prednisone alone, limiting a full evaluation of the benefit of MMF. ($55.001)

**NEURO-OOTOLOGY**

G. Michael Halmagyi and colleagues (Sydney, Australia) reported the utility of the horizontal head impulse test (HIT) to detect gentamicin-induced vestibulotoxicity. In the HIT, the patient’s head is rapidly rotated by the examiner while the patient fixates on the examiner’s nose. If there is a deficit in the vestibulo-ocular reflex, one sees a refixation saccade at the end of the rotation. The authors quantified vestibulotoxicity by measuring the gain of the horizontal vestibulo-ocular reflex (VOR) at different accelerations (750 patients demonstrated an essentially symmetric deficit of HIT gain along a continuous spectrum from normal to complete bilateral vestibular loss). The deficits occurred even at the slowest head accelerations. Across subjects, HIT gain correlated better with caloric testing ($r = 0.85$, $P = 0.0001$) than with rotational testing ($r = 0.55$, $P = 0.046$). The cumulative amplitude of overt catch-up saccades was 5.6 times greater in patients than in control subjects. The authors concluded that the horizontal HIT is a sensitive measure of gentamicin-associated vestibulotoxicity. ($57.001$)

Jorge Kattah and colleagues (Peoria, IL) studied the localization of vertiginous attacks in patients with acute vestibular syndrome (AVS) in a cross-sectional study over 9 years. Their cohort consisted of consecutive patients with AVS who presented with vertigo, nausea/vomiting, unsteady gait, and/or head motion intolerance and had at least one stroke risk factor. They underwent structured examination, including horizontal HIT and cover testing for ocular alignment, within 72 hours of symptom onset, and neuroimaging. CNS causes were confirmed by MRI or CT. A total of 101 patients with AVS were enrolled, of whom 25 had a peripheral vestibulopathy and 76 had a brainstem cause (72 ischemic strokes, 2 demyelinating lesions, 1 hemorrhage, and 1 anticonvulsant toxicity). Skew deviation (mean 9.9 prism-diopters, range 3-20 prism-diopters) was present in 15% of the total study population and correlated with brainstem involvement: it occurred in 4% (1 of 25) with a peripheral lesion, 4% (1 of 28) with pure cerebellar lesions, and 27% (3 of 48) with a brainstem lesion ($P = 0.004$). Of note, the presence of skew deviation correctly predicted the presence of lateral pontine stroke in 2 of the 3 patients in whom positive results for a horizontal HIT had suggested a peripheral cause. The authors concluded that although skew deviation is an insensitive marker of central pathologic changes, when it is detected it is reasonably specific for brainstem involvement among patients with AVS. ($57.002$)

David Newman-Toker and colleagues (Baltimore, MD) evaluated the cost-effectiveness of diagnostic decision support (DDS) relative to current clinical practice for identifying stroke among patients with dizziness in the emergency department (ED). DDS systems are interactive computer programs that use a software algorithm and patient data to suggest diagnoses that assist the clinician. The authors evaluated DDS by combining literature and expert-derived estimates of probabilities and utilities with local hospital cost estimates to compare hypothetical diagnostic strategies. The base case was a 65-year-old patient in average health without disability presenting either with new persistent dizziness (>24 hours, at risk for stroke) or new transient dizziness (<24 hours, at risk for transient ischemic attack [TIA]). The alternative diagnostic strategies were “CT all,” “MRI all,” and “admit all.” Outcome measures were cost, quality-adjusted life-years (QALYs) and incremental cost-effectiveness ratios ($/QALY$). The authors found that for persistent dizziness, DDS operating at 92% sensitivity and specificity ($10,400/QALY$) or “MRI all” ($12,200/QALY$) could outperform current practice at acceptable cost. “CT all” would be less effective and “admit all” would not be cost-effective ($190,000/QALY beyond “MRI all”). For transient dizziness, DDS operating at 85% sensitivity and specificity ($81,400/QALY$) could outperform current practice at moderately acceptable cost. “CT all” and “MRI all” would provide less quality for the cost, and “admit all” would not be cost-effective ($379,000/QALY beyond current practice). The authors concluded that bedside DDS could reduce cerebrovascular misdiagnosis among acutely dizzy patients at acceptable societal cost. ($04.083$)

Yoon-Hee Cha and colleagues (Los Angeles, CA) evaluated the association between benign recurrent vertigo (BRV) and migraine by studying 208 patients with BRV recruited through a university neurotology clinic with a standardized questionnaire-based interview. In their study, 180 of 208 patients (87%) met the International Classification of Headache Disorders 2004 criteria for migraine, 112 with aura (62%) and 68 without aura (38%); 28 (13%) did not meet criteria for migraine. Among patients with migraine, 70% experienced migraine symptoms (headache, aura, photophobia, or auditory symptoms) with some or all of their vertigo attacks, meeting the criteria for definite migrainous vertigo. The remaining 30% of patients did not experience concurrent migraine symptoms and vertigo. The
age of onset and duration of vertigo attacks did not differ significantly between patients with migraine (34 ± 1.2 years) and patients without migraine (31 ± 3.0 years). In patients with migraine, the age of onset of migraine headache preceded the onset of vertigo spells by an average of 14 years and aura preceded vertigo by 8 years. The duration of vertigo attacks was generally between 1 hour and 1 day. The authors concluded that the high association between BRV and migraine favors its recognition as a migraine equivalent syndrome. However, many patients with BRV and migraine never have migraine symptoms during the actual vertigo attack. The recognition of vertigo attacks as part of a migraine syndrome may be obscured by its later onset relative to the onset of headache and auras. (S46.002)

**MISCELLANEOUS TOPICS**

Suzanne Lesage and colleagues (Baltimore, MD) evaluated the correlation between retinal vascular abnormalities and cognition in elderly individuals. They studied 803 participants within a prospective community population study (Atherosclerosis Risk in Communities [ARIC]). Cognitive assessments included word fluency (WF), digit symbol substitution (DSS), and delayed word recall (DWR). Retinal photographs were evaluated for small microaneurysms or hemorrhages. WF scores declined to a greater degree in people with retinopathy than in those without retinopathy (1.64 [95% CI 3.3 to 0.02] and +0.06 [95% CI 0.6 to 0.8], respectively), even after adjustment for diabetes, hypertension, smoking, and apolipoprotein E allele status. Individuals with retinopathy had increased odds (2.18 [95% CI 1.02–4.64]) of having the greatest decline on DSS. There was no association between DWR performance and retinal vascular abnormalities. The authors concluded that microvascular retinopathy correlates with cognitive measures in elderly individuals, possibly by serving as a marker for cerebral vascular disease. (P09.126)

Thomas Buchanan and colleagues (Salt Lake City, UT) conducted an 8-year retrospective chart review to assess the demographic features of individuals with the diagnosis of photophobia. They examined other underlying diagnoses, employment status, treatments, and outcomes. The population included 63 women and 61 men, with a mean age at presentation of 37 years (range 6 months–94 years) and mean age of 27.3 years at onset of photophobia. Photophobia was most often attributed to migraine (49.2%), followed by dry eye syndrome (35.5%), progressive supranuclear palsy (8.1%), prior eye trauma (7.3%), prior head trauma (4.8%), and other ocular conditions, including blepharitis (12.9%). No cause was found in nearly 25% of the patients, among whom most were children. Among these patients, 24% reported that the symptom interfered with quality of life and 7.4% reported depression. Glasses with FL-41 tint were prescribed for almost 50% of the patients, among whom a majority reported benefit. The authors concluded that photophobia affects a diverse population and is associated with a variety of diagnosable conditions, including headache, traumatic brain injury, and other neurologic and ocular diseases. Depression and reduced quality of life were very common among these patients. (P04.078)
Common Neuro-Ophthalmic Pitfalls: Case-Based Teaching


Scope: With a case-based approach, this book is intended to bridge the gap between textbook information and the everyday experience of practicing neuro-ophthalmologists.

Rather than the standard textbook organization by disease process, the book is divided into 12 chapters, each representative of a particular diagnostic challenge: when ocular disease is mistaken for neurologic disease; when orbital disease is mistaken for neurologic disease; mistaking congenital anomalies for acquired disease; radiographic errors; incidental findings; failure of pattern recognition; clinical findings that are subtle; misinterpretation of visual fields; neuro-ophthalmic look-alikes; over-reliance on negative tests; over-ordering tests; and management misadventures.

Several cases are presented in each chapter to illustrate diagnostic principles of common and sometimes confusing neuro-ophthalmic disorders, and the text is generously supplemented with illustrative figures and useful tables. Summarizing tips are provided at the end of each case discussion, highlighting the key aspects of the clinical presentation. In cases of unusual neuroimaging abnormalities, normal images are provided for side-by-side comparison. A list of suggested reading is provided at the end of each chapter.

Strengths: The novel organization, carefully chosen cases, and clarity of writing are all highly effective in creating a wonderfully readable text. Cases are presented as unknowns, and questions are posed as the case unfolds to make them challenging and interactive. Many of the conditions or presentations are compared in ways not found in any standard textbook. For example, transient monocular visual loss from corneal disease is compared with the ocular ischemic syndrome. The critical importance of the history and examination in evaluating patients with neuro-ophthalmic disease becomes clear, with memorable clinical pearls shared from the collective experience of two master clinicians with an uncanny diagnostic acumen.

Weaknesses: It is hard to find fault with this book, which is the first medical book I have read that was not only informative but also enjoyable to read. Although there is some repetition of material in the case presentations found within the subsequent discussions, it does serve to reinforce the illustrative points of the cases.

Recommended Audience: This book achieves its goal of appealing to a broad audience, ranging from medical students and residents to practicing neurologists, ophthalmologists, neurosurgeons, neuroradiologists, and even seasoned neuro-ophthalmologists.

Critical Appraisal: The authors have accomplished the remarkable feat of writing a medical book that makes learning a complex subject both interesting and fun. The astute observations and clinical pearls underscore what the field of neuro-ophthalmology is all about. Although many outstanding neuro-ophthalmology textbooks exist, the authors have written a text that is sure to become a classic.

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Curbside Consultation in Neuro-Ophthalmology: 49 Clinical Questions


Scope: This is a text developed for ophthalmologists in a series that includes “curbside consultations” for many other subspecialties in ophthalmology. In this volume, the editors have compiled a list of 49 questions and posed them to master clinicians in the field of neuro-ophthalmology. Each question begins with a short clinical vignette. Examples of some questions that follow are: How should an optic glioma be managed? What neuroimaging studies should I order? Is there a difference in the management of pseudotumor in pregnancy? What is the evaluation of anisocoria? What is opsoclonus and how do manage it?

The contributing authors include, among others, Neil Miller, James Corbett, Nancy Newman, Steve Newman, Michael Wall, and Randi Kardon. Their answers are designed to meet four criteria: current, concise, credible, and clinically relevant. The book runs to 214 pages,
including the index. After each answer, there is a summary with bullet points and a few pertinent references.

**Strengths:** The authors have provided well-written responses that should offer excellent guidance to general ophthalmologists who grapple with these difficult issues.

**Weakness:** In any multiple-authored textbook, there is always some variability in the quality of chapters. Although this is the case here, I would rate all the chapters as very good to excellent.

**Recommended Audience:** In the preface, the editors point out that the target audience of the book is the practicing ophthalmologist. This is clearly a handy book for the practitioner to quickly consult when faced with one of the clinical questions. A secondary audience for the text is residents and fellows, who will also find it informative. For the neuro-ophthalmologist, most of the material would be well known. However, it is instructive to see how our colleagues are answering these curbside consultations.

**Critical Appraisal:** This is an excellent book that admirably achieves its purpose. It is highly recommended.

**Ophthalmology, 3rd Edition**


**Scope:** This multi-authored text provides a comprehensive review of ophthalmology, both in breadth and depth of coverage, and is sufficient to answer all but the most detailed subspecialty question. The authors follow the directive of the first two editions, aiming this text at trainees, non-ophthalmologists, and comprehensive ophthalmologists. The entries are not as detailed as in subspecialty publications, but the text is more manageable than multi-volume series and successful in providing most of the information needed for all but the most detailed reviews.

The book is organized into 12 parts by a blend of anatomy and subspecialty, with each part color-coded for ease of navigation. Each part is divided into chapters that use a consistent template to review a disease, procedure, or diagnostic test. Each chapter begins with a definition of the chapter title, key features, and associated features and is full of large, easy-to-read tables, color illustrations, and figures. The chapters are extensively referenced.

**Strengths:** The color-coding and chapter template format make the text easy to follow. The text is well illustrated with a multitude of large and visually appealing color figures that encourage the reader to peruse multiple chapter sections. The size and color of the photography move the reader along. There is excellent coverage of relevant basic science without being excessive and a consistent focus on advances in clinical conditions, diagnostics, and treatments. The sections on genetics, ophthalmic technology, immunology, and tuberculosis have been expanded. The book retains the size of previous editions due to rigorous purging of outdated material.

**Weaknesses:** This text is not able to attain an encyclopedic depth of each area and still remain as a single portable volume. That being said, the practitioner looking to review in such depth would be unlikely to choose a single textbook. Extensive references direct the reader elsewhere.

**Recommended Audience:** The authors have succeeded in reaching their target audience of trainees, non-ophthalmic physicians, and comprehensive ophthalmologists. Ophthalmic subspecialists would, however, also do well to obtain this text to review areas outside their area of expertise and will doubtless pick up pointers in their own field.

**Critical Appraisal:** This book deserves a place as the first source to review any area of interest or any point of uncertainty in clinical ophthalmology. The format allows quick access. It is well written and easily read, interesting, and full of excellent references.
typically found previously in such a text. Sections such as “Glaucoma in the World” and “Horizons” include public health, neuroprotection, and gene therapy. There are excellent sections on current imaging techniques.

The second volume encompasses established surgical therapy as well as newer therapies such as deep penetrating sclerectomy, and the EXPRESS mini shunt. It has detailed information on postoperative management and complications.

**Strengths:** The color coding of sections makes it easy to find them. Pictures and figures enhance the text. Colored text boxes for summaries and commentary of topics are helpful.

**Weaknesses:** The photographs are not of especially high quality. Some of the figures are too small.

**Recommended Audience:** This text is most suitable for ophthalmologists who have a serious interest in glaucoma or a need for a detailed glaucoma reference. Glaucoma fellows and training programs in particular would benefit from its information. It is quickly becoming my favorite text.

**Critical Appraisal:** The editors, who hail from four countries, have assembled an excellent international cast of authors and have provided a current comprehensive text on glaucoma, which is, after all, the most common optic neuropathy.

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**Pickwell’s Binocular Vision Anomalies, 5th Edition**

Bruce J. W. Evans, PhD, FCOptom.

**Scope:** This is the fifth edition of a text on the clinical and practical aspects of binocular vision originally written by Professor David Pickwell. The author, Bruce Evans, is the Director of Research at the Institute of Optometry in London. The basis of the text is to elaborate on Dr. Pickwell’s clinical and research experience. The author points out that many works in the field of optometric binocular vision, especially as they relate to behavioral vision therapy, were not performed using evidence-based approaches and thus may need to be revisited. He therefore tries to prioritize those methods and treatments that have been validated with double-masked, randomized, placebo-controlled trials.

The book is divided into four parts and includes an appendix, glossary, and references. It also includes a CD-ROM. Each condition is ordered to include a definition, investigation, evaluation, and management. The first part is an introduction to binocular vision anomalies and the general examination. The second part is dedicated exclusively to heterophoria. The third part concentrates on strabismus. The fourth part deals with incomitant misalignment and nystagmus.

**Strengths:** This is a compressed but well-written book that includes enough basic information to lead the reader into more extensive details about each subject. The text is excellent in describing details of how to perform certain tests in a cookbook fashion and then provides algorithms on how to interpret the tests and where to institute treatments. The exquisite details of technique for certain examinations are quite useful (retinoscopy, Maddox rod, and Hess and Lees screen). The tables and figures are easily interpretable and complement the text. At the end of each chapter are four or five clinical key points. For the optometric student or non-optometrist, the glossary is an excellent addition to quickly look up terms that might not be familiar. There are extensive references. In the field of amblyopia, the recent studies by the Pediatric Eye Disease Investigator Group are included.

**Weaknesses:** There is much in this work that is weakly supported by evidence, including vision therapy, the Meares-Irlen syndrome, and the use of colored lenses and inlays. In some instances the author is vague about the origin of certain diagnoses and makes scientifically unsupported assertions.

**Recommended Audience:** This text is primarily directed to students of optometry and optometrists. Pediatric ophthalmologists, neuro-ophthalmologists and orthoptists would gain in-depth knowledge of binocular vision testing and the optometric perspective. The focus on the United Kingdom providers is emphasized by the provision of a list of equipment suppliers in the UK and information on membership in the UK College of Optometrists. Also included are descriptions on the Diploma in Orthoptics of the College of Optometrists and Fellowship of the Royal College of Ophthalmologists.

**Critical Appraisal:** Despite its deficiencies, this is an excellent and useful text that elucidates the details of the optometric binocular vision examination and its interpretation. For pediatric ophthalmologists or neuro-ophthalmologists, the text provides useful details about
the diagnosis, management, and treatment of controversial disorders from an optometric perspective. Reading it would provide a basis for more congenial and productive interactions.

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Age-Related Changes of the Human Eye

Carlo A. P. Cavallotti, MD, PhD and Luciano Cerulli, MD, PhD, Editors.

Scope: This book forms part of a series on Aging Medicine™ that intends to offer clinical and research-oriented resources for physicians and researchers interested in aging medicine. The aim of this text is to provide a broad-based overview of the aging processes that occur in the human eye and to make this information accessible to specialists from all areas of ophthalmology.

The text is divided into 22 chapters, each dealing with a specific anatomic compartment. The editors begin with a chapter on “Aging as a Risk Factor in Eye Disease,” thus setting the stage for subsequent discussion. This is followed by individual chapters on age-related changes in the eyelid, optics of the eye, cornea, lens, trabecular meshwork, and iris. The second half of the text deals with the vitreous, retina, retinal pigment epithelium, choroid, and various pathologic states affecting the posterior segment. The remainder of the book deals with topics such as intraocular pressure and visual rehabilitation in elderly individuals. In each chapter, experts in their respective fields present a summary of the morphologic, physiologic, and biochemical changes that occur as a result of the aging process. Each chapter is preceded by an abstract that summarizes the main areas covered. Each chapter is also accompanied by black and white illustrations.

Strengths: The book is concise and relatively easy to read. Many of the chapters include comprehensive bibliographies that may serve as a launching pad for more detailed literature searches. Many of the authors also provide personal experimental data. A number of chapters stand out for their comprehensive approach, such as that on aging of the human lens.

Weaknesses: The book is hampered by spelling and grammatical errors. There are also a few factual errors and inconsistent use of terminology (“latex degeneration” vs. “lattice degeneration”). The book’s main weakness, however, is the uneven quality of the content. There is also a considerable degree of overlap between the chapters, and some chapters in the latter half of the book may be of little interest to ophthalmologists. Curiously, the chapter entitled “Treatment of Intraocular Pressure in Elderly Patients” deals solely with the results of a study on the effects of systemic antihypertensive drugs on intraocular pressure.

Recommended Audience: This book is likely to be of most interest to graduate students and as an introductory text for basic or clinical research.

Critical Appraisal: Many aspects of the text are appealing, but there are some drawbacks in the execution that must be rectified in subsequent editions.

Artificial Sight: Basic Research, Biomedical Engineering, and Clinical Advances

Mark S. Humayun, MD, PhD, James D. Weiland, PhD, Gerald Chader, PhD, and Elias Greenbaum, PhD.

Scope: This book offers an overview of the research sponsored by the United States Department of Energy (DOE) in support of a consortium that includes Second Sight Medical Products, Inc., University of Southern California, Oak Ridge National Laboratory and their related colleagues, and other researchers invited to make presentations at the Second DOE International Symposium on Artificial Sight. The researchers who were not sponsored by the DOE represented the work of six groups of researchers from three countries outside the United States. Their inclusion is consistent with the spirit of the DOE to promote international cooperation in the pursuit of new technologies.

A wide range of engineering and biologic topics is represented, including computational models of electromagnetic and thermal effects in the eye, systems designs for retinal prosthetic devices, development of new devices for use with retinal prosthesis, in vitro retinal physiology,
biologic responses to electrical stimulation, and matters related to human testing.

Strengths: Despite the large number of authors, the quality of the scientific presentation is very good. The authors and editors have made this widely disparate scientific material understandable to readers who are not part of the field of visual prosthetics. There is effective use of illustrations. The initial chapter of the book, which is written by some of the editors, provides a well-balanced overview of biologic considerations for an intraocular retinal prosthesis. The authors were astute in also covering the disadvantages of retinal or optic nerve prosthetic devices. The chapter by Horning and colleagues provides a manageable overview of the design of one type of prosthetic device, a description of some special technologies that have been developed by IMI Intelligent Medical Implants GmbH, including the “retina encoder” designed to help improve the quality of visual images after a prosthetic device is implanted. The book also provides a strong overview of the engineering challenges.

Weaknesses: Neither the biologic nor engineering chapters contain sufficient detail for the advanced reader. The retinal encoder chapter could have included a more substantial description of preclinical studies needed to obtain regulatory approval to perform human tests. This topic should have had a chapter of its own. There is insufficient discussion of the results of human testing after chronic implants of retinal prosthetic devices.

Recommended Audience: This book has material that will be of interest to electrical and materials science engineers, visual neuroscientists, and physicians, especially ophthalmologists who care for patients who are potential candidates for visual prosthetic devices. For young scientists, it will be illuminating in terms of the shear scope of activities needed to create an implantable device for this purpose. For young physicians, it will provide variable insight into the engineering infrastructure that is needed to attempt to build sophisticated, implantable bi-electronic devices. For experienced clinicians, it will provide insight into the challenges of attempting to restore vision to the blind.

Critical Appraisal: This is an excellent overview of progress on retinal and optic nerve visual prostheses. After reading it, you will be able to provide some hope to your patients by being familiar with the research in this area, and you also come away with a more realistic view of when and to what extent devices of this nature will be of value.

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The Confabulating Mind: How the Brain Creates Reality

Armin Schnider, MD.

Scope: The author has produced an invaluable contribution to the literature in cognitive neuroscience with his textbook on confabulation, the unintentional production of false memory. The ability to distinguish between real and illusory components in human percepts has been a key issue in the development of cognitive neuroscience, yet has been paid scant attention in recent publications. This fact may seem surprising given the extensive literature on false production of memory from the early 1880s through the 1960s. However, most early writings on the topic were in German or French and were therefore to some extent ignored in the English literature.

Strengths: Because of the author’s familiarity with English, German, and French, he has been able to meticulously analyze most of the publications on confabulation in their original language. He provides us with extensive quotations from papers dealing with the topic, as well as selected excerpts from the early literature that he has himself translated into English.

He guides us through the subtle and exciting changes that have taken place with regard to the definition and pathologic interpretations of the concept of confabulation, from Kraepelin’s idea of deficient critical sense (1886), to Korsakoff’s hypothesis of anterograde and retrograde amnesia, acute confusion, and disorientation (1899), Van der Horst’s claims that confabulation was the clinical expression of a gap-filling phenomenon (1932), and contemporary controversies on the topic.

The volume is divided into nine chapters. Chapter 1 contains an introductory case report that illustrates the problem of confabulation. Chapter 2 discusses the history of ideas on confabulation, the ideas of suggestibility, theories and mechanisms behind gap-filling, and the role of toxic substances such as alcohol in the generation of confabulation. Chapter 3 discusses the various definitions of confabulatory clinical presentations, including diagnosis of behaviorally spontaneous confabulation and provoked vs. spontaneous confabulation. Chapter 4 reviews the etiologies and anatomic lesions resulting in confabulation. Chapter 5 describes disorders associated with or induced by confabulation, such as amnesia, disorientation, false recognition, paramnesia, misidentification, and anosognosia. The fascinating Chapter 6 covers false memories syndrome in healthy individuals, flashbulb memories, the distinction between normal false memory and pathologic confabulation, and the various ways
to manipulate eyewitnesses. Chapter 7 analyzes the mechanisms believed to underlie confabulation: gap-filling, alteration in personality and motivation, the executive hypothesis, reality and source monitoring, memory reconstruction and monitoring, the strategic retrieval hypothesis, and evolution of consciousness over time. Chapter 8 is devoted to the author's own research on behaviorally spontaneous confabulation and reality, including experimental results memory selection, clinical course and rehabilitation, evoked potential and imaging studies indicating early memory filtration, the possible nature of subcortical participation in memory selection, and a model of an online filter of reality in thinking. Chapter 9 deals with the anatomy and function of the orbitofrontal cortex and proposes a hypothesis linking extinction capacity—an orbitofrontal faculty—to reality control in thinking.

**Strengths:** The author's broad grasp of neurophysiology, clinical neurology, neuropsychology, and neuro-imaging results in an in-depth presentation of the pathophysiology and subtle clinical variations of confabulation, their anat-omopathologic correlations, and options for rehabilitation. The volume also includes an exciting chapter on confabulation in normal individuals and on ways of modulating memories or inducing false memories. These issues have major implications, as in altering visual memories in witnesses at trial.

**Weaknesses:** There are none.

**Recommended Audience:** Clinicians and researchers interested in the foundations of cognitive neurosciences will find this book a captivating addition to their library.

**Critical Appraisal:** This is a beautifully presented, clearly illustrated, extensively referenced, and well-indexed volume. It reflects the breadth and depth of the author's scholarly personality, extensive clinical experience in neurology and neuropsychology, rigorous and comprehensive approach, and didactic ability. It has an essential place in the literature of cognitive neuroscience and should be required reading for those involved in the study of confabulation.

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**Mayo Clinic Essential Neurology**

Andrea C. Adams, MD.  

**Scope:** This is a concise 392-page clinical neurology textbook focused on the most common adult neurologic symptoms. There are 14 chapters devoted to the evaluation and treatment of headache, back and limb pain, dizziness, sensory loss, weakness, cognitive loss, spells, pain, cerebrovascular disease, movement disorders, and immune, infectious and oncologic diseases. The first two chapters review the key principles of a thorough neurologic examination and of the primary diagnostic tests.

**Strengths:** The author’s keen experience as a clinician educator is well demonstrated. She skillfully selects the most important diseases and concisely crystallizes the most important evaluative and therapeutic points. All chapters are comprehensive without over-accentuating the neuroanatomy correlation. Highlights are the chapter on “Spells,” which covers the topics of epilepsy and sleep disorders, and the chapter on “Headache.” Both include excellent summary tables of therapeutic options including side effect profiles. The illustrations are colorful, appealing, and underscore the text well, whether it be a localization point, a brain CT scan, or a muscle biopsy. The length of the textbook is manageable, and it is very readable.

**Weaknesses:** There are no representative clinical case studies. Although the author may have intentionally left them out to achieve a concise textbook, clinical case studies often provide a good introduction to neurology for the novice. The essentials presented in this textbook will be easily mastered by neurology-oriented residents-in-training, so the “Recommended Reading” section at the end of each chapter is an important feature. Because the neuro-infectious and neuroimmunologic diseases are combined in one chapter, details in this section are sparse. For example, herpes virus is mentioned only in a table. A pithy discussion could be added to underscore important clinical clues (seizure or psychiatric presentation, brain MRI, electroencephalogram, and cerebrospinal fluid findings) in this life-threatening condition. A brief discussion of classic clinical symptoms and signs of prion disease would have been welcome. Stand-alone chapters for these topics are suggested for further editions.

**Recommended Audience:** All students, residents, and fellows in the medical neurosciences, as well as physicians or health care personnel providing neurologic outpatient care in family practice, hospital, and paramedical settings would find this book useful.

**Critical Appraisal:** This textbook stands out for its abundant informative color illustrations, succinctly written text supplemented with tables, and manageable length. It is destined to move to the foreground of textbooks for teaching fundamental concepts in neurology. It has appeal to medical students, residents-in-training in neuroscience-based
disciplines, family practice physicians, and those in other primary care settings.

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Little Black Book of Neurology, 5th Edition

Osama O. Zaidat, MD and Alan J. Lerner, MD.  

Scope: This pocket book aims to be a portable, yet comprehensive, guide to clinical neurology. It is organized alphabetically by topic with plenty of figures and tables. This most recent edition has several useful appendices, including summaries of clinical guidelines from the American Academy of Neurology, neurologic emergencies, therapeutics, and clinical scales. In this edition, the authors have added new information and updated references.

Strengths: Unlike my well-worn copy of the 3rd edition, this edition has a useful table of contents and an index that make it considerably easier to find information. It continues to have numerous outstanding figures and tables, such as those covering cerebral arterial and venous anatomy, the cerebellum, pediatric norms, cerebrospinal fluid, channellopathies, and paraneoplastic diseases. The new appendices are excellent additions that offer rapid therapeutic guidance.

Weaknesses: Although this book succeeds in covering the full breadth of topics relevant to clinical neurology in such a small space, it loses considerable detail and nuance in the evaluation and treatment of many neurologic diseases because of space limitations. Furthermore, residents and junior neurologists are the principal authors of the book, leading to some odd oversights, such as separate headings for idiopathic intracranial hypertension and pseudotumor cerebri which contain slightly different advice and nary a cross-reference to each other.

Recommended Audience: This book is aimed directly at the neurology resident and serves as a good, basic, ready reference for the broad range of conditions encountered on the wards and in the clinic. Residents in allied fields, such as neurosurgery, neuroradiology, and medicine, may also find it useful.

Critical Appraisal: For neurology residents, this is a pocket guide that is worth weighting down their white coats, but it is hardly the final source.

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Neurologic Complications of Cancer, 2nd Edition

Lisa M. DeAngelis, MD and Jerome B. Posner, MD.  

Scope: This is the 2nd edition of a text that appeared in its 1st edition in 1995. It is part of the venerable Contemporary Neurology Series that began more than 50 years ago with The Diagnosis of Stupor and Coma, authored by Fred Plum, MD, and Jerome Posner, MD, who is also the second author of this book.

This edition and the original edition are meant to complement texts on primary brain and spinal cord tumors by dwelling on parenchymal, leptomeningeal, and dural metastases, primary tumors of the cranial and spinal nerves, and nonmetastatic effects such as intracranial and spinal infarction and hemorrhage, infection, metabolic, nutritional, and paraneoplastic disturbances, as well as side effects of radiation and chemotherapy. The authors, who are based at Memorial Sloan-Kettering Cancer Center in New York City, draw on the published literature and on their extensive experience as neuro-oncologists.

Running to well over 600 pages, this edition is nearly twice as thick as the original. The new material comes mostly from the reporting of new modes of therapy, as well as from an attempt to explain the pathophysiology of metastatic and nonmetastatic manifestations.

Strengths: The authors are academic giants who have seen more cases, published more studies, and trained more neuro-oncologists than anyone else in the world. Thus, the information they impart is as reliable as you will find anywhere—and very useful. For example, you will find out the comparative value of MRI and spinal fluid analysis in the detection of leptomeningeal cancer. You will learn which corticosteroid side effects to expect, how often, why, and what to do about them. The sections on radiation and chemotherapeutic complications are definitive. Not surprisingly, the chapter on paraneoplastic manifestations is a gem, as the authors are originators in this field.
The text is well-written and nicely edited. These features are due in part to the fact that Oxford University Press, with its devotion to high publishing standards, has taken over the Contemporary Neurology Series. The tables and illustrations are aptly chosen and gracefully spaced to highlight and break up the monotony of text. The color figures are a welcome addition.

**Weaknesses:** The subject matter is somber. There is no good news for the patient. The truth is that in the 13 years since the first edition has appeared, very little therapeutic progress has been made. Much of this material is available in separate sources, some of it is conveniently online.

**Recommended Audience:** Although the text is aimed at neurologists and neuro-oncologic nurses, anyone who deals with cancer will find this a valuable resource.

**Critical Appraisal:** For information about metastatic brain and spinal cancer and its effects, there is no better source. Given the changing habits of information-seeking by physicians, who are relying more and more to online sources for quick tips, one wonders how much traffic this book will get. It is heavy in weight and tone and cannot be easily updated. Yet it is a beautiful rendering of the incomparable clinical experience and academic prowess of two of the most learned specialists in the field. Institutional libraries and seasoned neurologists know the quality of the Contemporary Neurology Series. They will—and should—go for it.

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**Vascular Neurology: Questions and Answers**

Nancy Futrell, MD and Dara G. Jamieson MD.

**Scope:** This is a study guide presented in question-and-answer format for physicians preparing for board certification by the American Board of Psychiatry and Neurology (APBN) in vascular neurology. It contains more than 500 questions and is divided into nine sections, covering basic sciences and clinical topics. One third of the book is devoted to clinical stroke, but the authors also cover basic science, cardiology, hematology, pediatric stroke, pathology, imaging, pharmacology, and rehabilitation.

**Strengths:** This study guide is comprehensive, well-written, and easy to read. Most sections reference pertinent and appropriate literature in the field. Questions and answers provide a good review of the basic science, epidemiology, pathophysiology, evaluation, treatments, and outcomes. Questions are quite representative of those found on the APBN board. Particularly strong sections are those on clinical stroke, pharmacology, rehabilitation, and pathology.

**Weaknesses:** Although the text deals mostly in well-accepted and scientifically based evidence, the authors occasionally present personal cases and anecdotes as definitive practice. The basic science section has very little anatomy and not enough illustrations. Many of the black and white images are of poor quality. The cardiology and hematology sections rely heavily on single texts for references.

**Recommended Audience:** This book successfully targets its intended audience of those preparing for the vascular neurology board examination, but residents preparing for the general neurology APBN board examination will probably find this book useful as well.

**Critical Appraisal:** This book fills a much-needed niche. It is thorough, relevant, accessible, and worth reading. However, its value is slightly diminished by the low quantity and uneven quality of photos as well as the authors’ occasional use of personal anecdotes.

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Irene E. Loewenfeld, PhD died suddenly of coronary artery disease on October 9, 2009 in New York, NY. She was 88 years old. She had a long, happy, and productive academic career thinking about how and why the pupils change their size.

She was born into a middle class German Jewish family in 1921. Her grandfather, Theodor Loewenfeld, was a law professor at the University of Munich, and her father was a well-established lawyer practicing in Munich. Nazi policies led to the family’s escape from Germany to Switzerland in 1934 and their eventual emigration to New York in 1939.

Dr. Loewenfeld was 19 years old when she took a technician’s job in Professor Otto Löwenstein’s pupillographic laboratory at New York University. She was soon making important contributions to Lowenstein’s pupillary projects. This work led to a lifelong fascination with the mechanisms of pupillary movements (documented in *Journal of Neuro-ophthalmology* 2006;26(2):139–148).

One of her great gifts to the world was the 25 years of her life that she devoted to her magnum opus: *The Pupil, Physiology and Clinical Applications*, Iowa State University Press, Ames, Iowa, 1993. A massive text in two volumes with 15,000 references and countless tables, it covers pupil matters as never before and perhaps never again (see book review in *Am J Ophthalmol* 1993;116:117–119).

**H. Stanley Thompson, MD**

Iowa City, Iowa
Upcoming Meetings

American Society of Neuroimaging 33rd Annual Meeting
San Francisco, CA
Contact: asn@llmsi.com

Jan. 21–Jan. 24, 2010
Joint Meeting of the 68th Annual Conference of All India Ophthalmological Society
15th Afro-Asian Congress of Ophthalmology
Science City, Kolkata, India
Contact: secretariat@aioc2010.com

Feb. 24–Feb. 26, 2010
International Stroke Conference
San Antonio, TX
http://strokeconference.americanheart.org/
Contact: strokeconference@heart.org

Mar. 6–Mar. 12, 2010
Tucson, AZ
http://www.nanosweb.org/meetings/nanos2010/
Contact: info@nanosweb.org

Mar. 23–Mar. 26, 2010
19th Annual Meeting of the Imaging and Perimetry Society
Puerto de la Cruz, Tenerife, Spain
http://www.ips2010.es/
Contact: ips2010@ips2010.es

Apr. 10–Apr. 17, 2010
American Academy of Neurology Annual Meeting
Toronto, ON
http://www.aan.com/go/am10
Contact: memberservices@aan.com

Apr. 14–Apr. 18, 2010
American Assn. of Pediatric Ophthalmology and Strabismus (AAPOS) Annual Meeting
Orlando, FL
http://www.aapos.org/
Contact: aapos@aoa.org

May 1–May 5, 2010
American Association of Neurological Surgeons
Philadelphia, PA
http://www.aans.org/annual/default.asp
Contact: info@aans.org

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

May 15–May 20, 2010
48th American Society of Neuroradiology (ASNR) Annual Meeting
Boston, MA
http://www.asnr.org/2010
Contact: meetings@asnr.org

May 25–May 28, 2010
European Stroke Conference
Barcelona, Spain
http://www.eurostroke.org/PDF/ESC10_FA.pdf
Contact: Hennerici@eurostroke.org

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

June 8–June 11, 2010
Canadian Neurological Sciences Federation 45th Annual Congress
Quebec City, Quebec, Canada
http://www.cnsfederation.org/general_information_congress.html
Contact: info@cnsfederation.org

June 15–June 18, 2010
18th International Neuro-Ophthalmology Society (INOS) Meeting
Lyon, France
http://www.inos2010.org/
Contact: inos2010@carco.fr
### June 19–June 22, 2010
**Society of Neurological Surgeons Annual Meeting**
New Haven, CT
http://www.societyns.org/meeting_info.html

### June 19–June 23, 2010
**20th Meeting of the European Neurological Society**
Berlin, Germany
http://www.congrex.ch/ens2010/
Contact: info@ensinfo.org

### June 26–June 29, 2010
**Canadian Ophthalmological Society Annual Meeting**
Quebec, Quebec
http://www.eyesite.ca/english/amindex.htm
Contact: cos@eyesite.ca

### July 3–July 7, 2010
**Forum of European Neuroscience Societies (7th)**
Amsterdam, The Netherlands
http://fens2010.neurosciences.asso.fr/
Contact: email form on above website

### July 9–July 16, 2010
**International Society on Metabolic Eye Disease**
Vancouver, Canada (cruise to Alaska)
http://www.continuingeducation.net/coursedetails.php?
program_number=797
Contact: 070910MetEye@continuingeducation.net

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

### July 18–July 23, 2010
**XIX Biennial Meeting of the International Society for Eye Research**
International Congress on Eye Research (ICER)
Montreal, Canada
http://www2.kenes.com/isrer/Pages/Home.aspx
Contact: isrer@kenes.com

### Sept. 11–Sept. 15, 2010
**XVIth International Congress of Neuropathology**
Salzburg, Austria
http://www.icn2010.org/
Contact: daniela.gaertner@meduniwien.ac.at

### Sept. 12–Sept. 15, 2010
**135th Annual Meeting of the American Neurological Association**
San Francisco, CA
FutureMeetings
Contact: anameeting@llmsi.com

### Sept. 25–Sept. 28, 2010
**14th Congress of the European Federation of Neurological Societies (EFNS)**
Geneva, Switzerland
http://www.efns.org/14th-EFNS-Congress-Geneva-2010.365.0.html
Contact: headoffice@efns.org

### Oct. 6–Oct. 9, 2010
**European Association for Vision Research (EVER) Annual Congress**
Crete, Greece
Contact: ever@ever.be

### Oct. 13–Oct. 16, 2010
**7th World Stroke Congress**
Seoul, Korea
http://www2.kenes.com/Stroke/Pages/Home.aspx
Contact: stroke2010@kenes.com

### Oct. 16–Oct. 19, 2010
**114th American Academy of Ophthalmology Annual Meeting**
Chicago, IL
http://www.aao.org/meetings/annual_meeting/chicago.cfm
Contact: meetings@aao.org

### Oct. 16–Oct. 21, 2010
**60th Annual Meeting of the Congress of Neurological Surgeons**
San Francisco, CA
Contact: info@1cns.org

### Nov. 13–Nov. 17, 2010
**40th Annual Meeting of the Society for Neuroscience**
San Diego, CA
Contact: info@sfn.org

### June 4–June 7, 2011
**18th Congress of the European Society of Ophthalmology Joint Meeting with the American Academy of Ophthalmology**
Geneva, Switzerland
http://www.soe2011.org/
Contact: soe2011@congrex.com

### July 14–July 19, 2011
**8th IBRO World Congress of Neuroscience**
Florence, Italy
http://www.ibro2011.org/site/home.asp
Contact: ibro2011@newtours.it