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Managing Carotid-Cavernous Fistulas in Ehlers-Danlos Syndrome Type IV

Phillip D. Purdy, MD

In this issue of Journal of Neuro-Ophthalmology (pp 102–106), Hideki Chuman, MD, PhD, Wayne T. Cornblath, MD, Jonathan D. Trobe, MD, and Stephen S. Gebarski, MD, describe two cases of Ehlers-Danlos IV (EDS IV) that presented with direct (spontaneous) carotid cavernous fistulas. In the first case, the clinical diagnosis of EDS IV was made between the time of the diagnostic arteriogram and the time of the treatment. In the second case, the diagnosis of EDS IV was confirmed by punch biopsy after the endovascular treatment. Both cases were treated by transvenous deposition of coils in the cavernous sinus.

The authors’ review of the literature regarding EDS IV is both timely and enlightening for those involved in the care of these patients. Given the frequency of presentation with carotid cavernous fistula, and the prominence of neuro-ophthalmologists in the early care and identification of this disease, familiarity with this clinical circumstance is certainly warranted in this community.

The emphasis of the authors on the hazards and pitfalls in this disease is appropriate. By virtue of the genetics and vascular practices at our facility, we also have had occasion to observe several patients. One is tempted to say they should be followed by magnetic resonance angiography (MRA), and their initial evaluation should include this technique. However, given the prevalence of intracerebral aneurysms in this disease, patients often have aneurysm clips that preclude routine MRA. Their need for long-term care and careful clinical follow-up is underscored by their propensity to develop new intracerebral aneurysms.

Two of our cases with less fortunate outcomes than those presented here come to mind in emphasizing the hazards of this disease and the importance of delicacy in its management. In one patient, I had performed multiple arteriograms over several years because of the development of many intracranial aneurysms. She had also developed a carotid-cavernous fistula, which had been successfully treated. However, her fistula recurred. At the end of diagnostic catheter cerebral angiography, she developed an iliac artery tear where the catheter had dwelt. The extravasation was emergently treated with stent placement but the iliac artery began leaking at the ends of the stent. She was taken to the operating room emergently, where she began hemorrhaging uncontrollably from multiple venous sites and eventually died.

In another patient, following diagnostic cerebral angiography, a splenic artery ruptured even though that vessel had never had a catheter or guidewire placed in it. Again the patient died.

In spite of short-term endovascular triumphs, the long-term prognosis remains very guarded. I support the use of a transvenous approach with coil deposition as the safest among a group of unsafe available choices. Unfortunately, the transvenous route is not universally available, because some patients with direct carotid-cavernous fistulas have lost...
their inferior petrosal sinuses. And although arterial fragility is well known in these patients, similar fragility affects the venous side (witness our patient above who developed venous bleeding from multiple sites in the operating room).

When a neuro-ophthalmologist first encounters a possible EDS IV patient, early consultation with an endovascular surgeon should be obtained with the aim of minimizing invasive procedures. MRA should be used to make a diagnosis of carotid cavernous fistula, in order that the catheter angiographic procedure may be reserved for the planned intervention. However, the coexistence of intracerebral aneurysms must be anticipated, and a full diagnostic angiographic procedure should be performed at the time of treatment, both for counseling and as a baseline for subsequent follow-up care.

The role of genetic counseling of these patients and their families is appropriately highlighted in this paper. Developments in gene therapy represent the best hope for greater normality in the lives of those afflicted with this dreadful condition.
Spontaneous Direct Carotid-Cavernous Fistula in Ehlers-Danlos Syndrome Type IV: Two Case Reports and a Review of the Literature

Hideki Chuman, MD, Jonathan D. Trobe, MD, Elizabeth M. Petty, MD, Ulrike Schwarze, MD, Melanie Pepin, MS, Peter H. Byers, MD, and John P. Deveikis, MD

Two unrelated adults with Ehlers-Danlos syndrome type IV developed acute unilateral ophthalmoplegia and ipsilateral headache as a consequence of spontaneous (nontraumatic) direct carotid-cavernous fistulas. Because the interventional radiologist suspected the diagnosis of Ehlers-Danlos syndrome type IV, the carotid-cavernous fistulas were closed via the venous rather than the more standard arterial route in an attempt to avoid arterial dissection or rupture. In any patient presenting with a spontaneous direct carotid-cavernous fistula, family history and clinical examination should be targeted toward a diagnosis of Ehlers-Danlos syndrome type IV because of risks attendant to angiography and repair of the fistula. For these patients, ancillary medical care must be approached cautiously to avoid hollow viscous rupture. Molecular tests can be used to confirm the diagnosis and provide family members with accurate genetic counseling and predictive genetic testing.


Direct carotid-cavernous fistulas (CCFs) are abnormal communications between the intracavernous carotid artery and the venous plexus of the cavernous sinus. Head trauma is the most common cause. Spontaneous (nontraumatic) direct CCFs develop in patients with intracavernous aneurysms, and in individuals who have connective tissue diseases that cause vascular wall fragility, especially the vascular type of Ehlers-Danlos syndrome, Ehlers-Danlos syndrome type IV (EDS IV) (1-4).

EDS IV is a highly penetrant, dominantly inherited connective tissue disorder that results from mutations in type III collagen gene, COL3A1. It is clinically characterized by easy bruising, translucent skin, acrogeria, distal joint hypereextensibility, and early mortality due to arterial and hollow organ ruptures (1,2). Unlike other types of EDS, EDS IV does not usually cause large joint laxity, delayed skin wound healing, or paper thin scars that lead to early medical diagnosis. Individuals without a known family history may not be recognized to have EDS IV, even when they present with a major vascular or hollow organ rupture or a spontaneous direct CCF. If the clinical diagnosis is not recognized, angiography and repair of the CCF may be undertaken without the special precautions that help to avoid the complications associated with these interventions in EDS IV (4).

We present two patients with EDS IV who developed spontaneous direct CCFs. Although there was a genetically confirmed diagnosis of EDS IV in the son of one patient, and a history of a spontaneous CCF in the sister of the other patient, in neither patient was the diagnosis of EDS IV confirmed when angiography took place. However, the interventional radiologist suspected the diagnosis and undertook fistula closure via the less conventional transvenous route to try to avoid the risk of arterial dissection and rupture in EDS IV.

CASE REPORTS

Case 1

A 57-year-old man developed sudden pain behind his OS and diplopia. The following day, he noted weakness on the left side of his face. Examination disclosed normal visual fields, partial left adduction, supraduction, and infrauction deficits, mild left upper lid ptosis, and left mydriasis with a sluggish pupillary reaction to light. Intraocular pressures were 15 mm Hg OU. The ocular adnexal, biomicroscopic, and fundus examinations were normal. He had incomplete weakness of all muscles of facial expression on the left, but preservation of remaining cranial nerves.
(including trigeminal). The rest of the neurologic examination was normal. He was referred to our institution for further evaluation and management.

A brain computed tomography (CT) scan was normal. Catheter cerebral angiography demonstrated a direct left carotid-cavernous fistula with predominant drainage through the petrosal sinus (Fig. 1A). Multiple aneurysms and dissections were present in abdominal and pelvic arteries (Fig. 1B). Following the angiogram, he developed a groin hematoma that did not resolve for several weeks.

The radiologist performing the diagnostic angiogram did not know that the patient was suspected of having EDS IV on the basis of clinical features and the fact that the diagnosis had been confirmed in his son some months earlier (Fig. 2). But with the discovery of the abdominal and pelvic aneurysms, a clinical diagnosis of EDS IV was made. Because of concern about arterial fragility in the region, platinum microcoils were placed via the inferior petrosal sinus into the cavernous sinus (Figure 1C), rather than using the usual transarterial placement of balloons. Once the coils were placed, a soft 4 French catheter was used for arterial injections of contrast to confirm that the fistula was occluded.

Postoperatively, he was treated with prednisone 60 mg/d to reduce inflammation in the thrombosed portion of the cavernous sinuses. Within hours of the procedure, periocular pain was gone. Six days later, his third nerve palsy had completely resolved; 10 days later, his facial palsy had

---

**FIG. 1.** Case 1: arteriogram. A: Left internal carotid arteriogram, lateral view, early arterial phase shows high-flow, direct carotid-cavernous fistula. B: Pelvic arteriogram, frontal view, shows aneurysmal dilatation of the common and external iliac arteries bilaterally, likely representing dissecting aneurysms (arrows). C: Left common carotid arteriogram, lateral view, shows complete closure of the carotid-cavernous fistula after transvenous deposition of microcoils in the cavernous sinus.
disappeared. Perhaps because of the corticosteroid treatment and increased constipation related to hospitalization, he ruptured his descending colon on the third postoperative day and required a colostomy. One year after the neurovascular procedure, there were no further complications. As anticipated, DNA testing later confirmed that the patient had the same COL3A1 mutation that caused EDS IV in his son.

The patient was born with bilateral equinovarus deformities requiring tendon release. From early childhood, he had experienced easy bruising and easily torn skin following mild abrasions or minimal bumping. He had had multiple right shoulder dislocations that ultimately required surgical repair and had a long history of adequately controlled essential hypertension. In 1998, he developed chest pain and a pleural effusion, was diagnosed with a pulmonary embolus, and had a Greenfield filter placed in his inferior vena cava.

The patient's mother had a history of early strokes and fragile skin but lived into her mid 80s (Fig. 2). His 32-year-old son had no significant joint hypermobility or skin abnormalities, but had developed a splenic infarct and angiographic evidence of multiple small aneurysms in abdominal arteries. On that basis, he was suspected clinically of having EDS IV. The diagnosis was confirmed by the analysis of type III procollagen produced by cultured skin fibroblasts (4). A splice site mutation in intron 8 of one allele of the COL3A1 gene (IVS8+5G→A) was found to be the causative mutation (Fig. 3). This mutation resulted in skipping exon 8 in the products of that allele and the encoded protein was then not properly functional.

Prior to his presentation with a CCF, the patient was notified that his son had a confirmed diagnosis of EDS IV, but he elected to defer his own genetic investigation because of reimbursement issues. He had undergone a normal Duplex scan of his abdominal vessels.

Case 2

A 48-year-old woman developed left periorcular pain, blurred vision in the OS, and diplopia on left gaze. Two days later, she noted pulsatile tinnitus and left periorcular swelling. A brain CT scan showed enlargement of extraocular muscles in the left orbit and she was treated with intravenous corticosteroids for a presumed diagnosis of inflammatory orbitopathy.

Within 2 days of the onset of her ophthalmic manifestations, the patient's visual acuity had worsened to no light perception in the OS. Examination that day disclosed 20/20 visual acuity in the OD, no light perception in the OS, a complete left ophthalmoplegia, left mydriasis with a sluggish pupillary reaction to light, and a left afferent pupil defect. Intraocular pressures were 18 mm Hg OD and 60 mm Hg OS. She had 9mm of left axial proptosis with marked left lid and conjunctival swelling and exposure keratopathy. Fundus examination disclosed a central retinal artery occlusion in the OS. The ocular adnexal, biomicroscopic, and fundus examinations were normal in the right. The rest of the neurologic examination was normal.

Her skin was soft and velvety to touch but not translucent. Some history of excessive bruising was noted and was clinically observed in areas associated
A Case 1

Normal allele

pre-mRNA

\[
\begin{align*}
7 & \quad 8 \quad \text{gtaaag} \quad 9 \\
\end{align*}
\]

mRNA

\[
\begin{align*}
7 & \quad 8 & \quad 9 \\
\end{align*}
\]

Mutant allele

\[
\begin{align*}
7 & \quad 8 \quad \text{gtaaat} & \quad 9 \\
\end{align*}
\]

B Case 2

\[\text{COL3A1 Exon 32} \]

\[
\begin{align*}
\text{Proc1(III)} & \quad \text{Gly Ala Ala Gly Pro Pro Gly Pro Pro Gly} \quad \text{Gly Asp Lys} \\
\text{Normal allele} & \quad 5'- \text{GGTGCTGCTGGTCCTCCTGGGCCACCTGGT} \quad -3' \\
\text{Mutant allele} & \quad 5'- \text{GGTGCTGCTAGTCCTCCTGGGCCACCTGGT} \quad -3' \\
\text{Proc1(III)} & \quad \text{Gly Ala Ala Ser Pro Pro Gly Pro Pro Gly} \quad \text{Gly Asp Lys} \\
\end{align*}
\]

FIG. 3. Schematic representation of the alterations in the COL3A1 gene in Case 1 (A) and Case 2 (B). In Case 1, the mutant COL3A1 allele (right) harbors a donor splice site mutation in intron 8 (IVS8+5G→A) that abolishes normal splicing and results in skipping of exon 8 in the mRNA from that allele. In Case 2, there is a single nucleotide substitution in exon 32 of one allele that results in substitution of the glycine at position 544 of the triple helix by serine (G544S, with reference to the first glycine of the triple helix). The substitution interrupts the Gly-Xaa-Yaa repeat pattern in the triple helix, which is needed to allow proper folding of procoll(III) chains into the functional homotrimers of type III procollagen.

with venipuncture. She had mild distal hand and foot joint hyperextensibility.

Catheter cerebral angiography demonstrated a direct left CCF from rupture of a small cavernous carotid aneurysm (Fig. 4A). The fistula was successfully closed with transvenous deposition of microcoils in the cavernous sinus (Fig. 4B).

Within 2 days of the procedure, the patient’s left periocular pain was gone, intraocular pressures had normalized, and lid swelling, conjunctival chemosis, and ocular ductions had markedly improved. However, visual acuity in the OS did not recover and the left afferent pupil defect persisted.

The patient’s 43-year-old sister had developed a spontaneous direct CCF five years earlier, but neither the patient’s sister nor any family members had been evaluated for EDS IV (Fig. 5). The diagnosis of EDS IV was confirmed by analysis of the type III procollagen synthesized by cultured dermal fibroblasts using previously described methods (5). A mutation was identified in one COL3A1 allele that resulted in substitution of the glycine at position 544 of the triple helix by serine (G544S). This mutation disrupts the formation of the collagen triple helix and interferes with the secretion of the protein.

DISCUSSION

These two cases illustrate the importance of early intervention in CCF associated with EDS IV to preserve vision, and emphasize the possibility of using the venous route to close the fistula. Spontaneous (nontraumatic) CCF is one of the most common CNS vascular complications of EDS IV (3,7); although, as in both our patients, the diagnosis may not be known at the time of presentation. Case 1’s son had had the diagnosis of EDS IV confirmed but the patient was not recognized to have EDS IV until visceral angiography identified multiple aneurysms. This diagnosis prompted the use of the venous approach to occlude the
fistula because of concerns that the catheters used to place balloons could induce arterial tears. The subsequent angiography to confirm closure of the fistula was done using a small-diameter soft catheter to try to minimize the risk of additional vascular injury.

The hazards of delayed intervention are illustrated in Case 2. Within days of developing ophthalmoplegia, she proceeded to infarct her optic nerve and retina. It is possible that earlier intervention would have restored appropriate flow and diminished the likelihood of visual loss. Both patients had large volume cerebral venous drainage from the cavernous sinus, which, if left alone, could result in cerebral venous thrombosis and stroke.

No consensus on the best endovascular approach to closure of an EDS IV CCF has been reached. Almost 30 affected patients have been described (6–13), but fewer than a dozen cases have been reported in sufficient detail to evaluate the efficacy of different approaches. General anesthesia is recommended for patient comfort and safety because catheterization of the cavernous sinus can be painful, and catheters and embolic agents can be visualized better and placed more precisely in an immobile patient. About 80% of the attempts to use an endovascular approach have involved transarterial balloon embolization, with higher than 50% success rate and one death (8–11) related to rupture of extracerebral vessels (12). Transvenous balloon
embolization, a less popular approach, appears to have had a similar success rate, although only about 20% of the attempts used this route. Transvenous coil deposition, the method chosen for our patients, has been reported only once previously, with a successful result (8). Coils may be superior to a balloon in this condition because they are softer, easier to control, and exchangeable (8). Moreover, they allow the use of smaller delivery devices for insertion and exert less pressure on the sinus than balloons. One possible advantage of the transvenous route is that iatrogenic injury to a low-pressure vein might be less deleterious than injury to a high-pressure artery.

Given the arterial fragility, ectasia, and tortuosity in EDS IV, we think it is appropriate to consider coil deposition via the transvenous route in closing CCFs in these patients. The direct supraorbital and inferior petrosal sinus entries are unlikely to be successful (12). The difficulties encountered with arterial placement of balloons have already led to the use of detachable coils (8, 13). Small caliber delivery devices probably lower the complication rate. These innovations may be, in part, responsible for a reduced morbidity rate in the last 10 years (8–13). The transvenous approach is not without problems, as the venous tree is also fragile, and upstream pressure from the arterial tree may interfere with placement of the occluding devices.

EDS IV is called the “vascular type” because of the prevalence of arterial rupture, dissection, and fistula (1). Although there is significant inter- and intrafamilial variability in the clinical presentation, the mean age of a major complication is 25 to 28 years, the average age of death, most often due to arterial rupture, is 45 to 50 years (2). The average age at the time of the first vascular or visceral complication is 24 years, with 12% mortality. The risk of a major complication by age 40 is 80% (2). In a recent review of 419 patients (2), 70% of deaths were the result of arterial rupture, mostly of thoracic and abdominal vessels, but also of cerebral vessels. The most common nonlethal vascular complication in that series was CCF. Other complications included colon rupture and rupture of the uterus during pregnancy. Pregnancy carries an 11% mortality rate from arterial or uterine rupture (2). Because EDS IV is uncommon, the identification of multiple arterial aneurysms may lead to a tentative diagnosis of vasculitis and treatment with immunosuppressive agents, which could compromise vascular integrity.

EDS IV is clinically distinct from other types of EDS in that affected individuals usually do not have large joint hyperflexibility or skin hyperextensibility (4). However, as illustrated by Case 1, dislocation of large joints can occur. Instead of skin hyperextensibility, patients with EDS IV often have translucent soft skin that bruises easily with minimal trauma. Acrogeric (prematurely aged) features involving the face and distal extremities are seen in some individuals with EDS IV, but were not present in either of our patients.

Given the subtlety of clinical features in some individuals, the physician should be alert to a family history of relatives with similar vascular problems or premature deaths due to arterial or hollow organ rupture. The diagnosis can be confirmed by analysis of type III procollagen produced by cultured fibroblasts, following which the mutation in the COL3A1 gene can be identified readily (2). Once a mutation is identified, other family members can be screened. Although no cure is available, confirmation of the diagnosis of EDS IV is critical in advising patients about the risks of pregnancy and in guiding medical and surgical therapy.
surgical management in the event of an arterial or hollow organ complication.

REFERENCES


Migraine-Like Visual Hallucinations in Occipital Lesions of Cysticercosis

Kumudini Sharma, MD, J. Wahi, MS, R. V. Phadke, MD, A. Varma, MS, and V. K. Jain, MS, MCh

Four Indian patients with occipital lesions of cysticercosis presented with visual hallucinations. Neuro-ophthalmic and systemic examinations were normal in all cases except for one patient who had a partial homonymous hemianopia. Electroencephalography was normal in all cases. Neuroimaging revealed ring-enhancing lesions in the occipital lobe typical of neurocysticercosis. In endemic regions like India, neurocysticercosis should be suspected in patients presenting with visual hallucinations, even when there are no other clinical findings.

(J Neuro-Ophthalmol 2002;22: 82-87)

CASE REPORTS

Four patients were examined in a neuro-ophthalmology clinic complaining only of seeing bright light on the lateral side of the field of vision. In two patients, this visual symptom was followed by a mild headache. Systemic examination was normal in all cases. Neuro-ophthalmic examination was normal in three patients, including visual fields, performed on a Tuccon automated perimeter using the full-field screening program. Sixteen-channel scalp electroencephalography (EEG) with photic stimulation was normal in all cases.

Computerized tomography (CT) or magnetic resonance imaging (MRI) disclosed enhancing lesions in the occipital lobe consistent with cysticercosis in all cases (Figs. 1-4). All patients were treated for cysticercosis with oral albendazole 15 mg/kg and oral prednisolone 1 mg/kg for 28 days. Carbamazepine was given in a dose of 10 mg/kg for 3 years as an anticonvulsant. Here are further details on each case (Table 1).

Case 1

An 18-year-old man complained of 2-minute episodes of seeing multiple, revolving, multicolored, round lights on the right side of his visual field. The lights started laterally in the right visual field and rapidly spread across the whole field. He described similar attacks three to four times per month for the previous 2 months. He was asymptomatic between attacks and had no complaints of headache, vomiting, convulsions, tingling and numbness, weakness in any part of the body, dizziness, or loss of consciousness. Systemic examination was normal. Visual acuity, color vision, ocular motility, pupillary reactions and fundus, and visual fields were normal. EEG with photic stimulation was normal. Brain CT revealed a 7-mm ring-enhancing lesion with perifocal edema in the left occipital region suggestive of a solitary degenerating cysticercus cyst (Fig. 1A). Once treatment was begun, the patient had no further visual hallucinations. A follow-up CT 2 months later showed resolution of the lesion (Fig. 1B).

Case 2

A 20-year-old man complained of 2-minute episodes of seeing a spinning, white, round, bright light with zigzag...
FIG. 1. Case 1. A: Enhanced axial computed tomography (CT) shows a ring-enhancing lesion with perifocal edema in the left occipital region consistent with a degenerating cysticercus cyst. B: Contrast enhanced axial CT after 2 months of treatment shows resolution of cyst.

FIG. 2. Case 2. A: Enhanced computed tomography (CT) shows a small ring-enhancing lesion in the left medial parieto-occipital region with perifocal edema extending to the occipital region. B: Enhanced CT after 2 months of treatment shows resolution of the cyst.
edges on the right side of his visual field. It expanded rapidly to occupy the whole visual field. The episodes had occurred twice per week for 2 months. Between attacks, he was asymptomatic. Systemic examination was normal. Neuro-ophthalmic examination was normal, including visual fields. Scalp EEG was normal. Contrast enhanced CT showed a 8-mm ring-enhancing lesion in the left medial parieto-occipital region with perifocal edema extending to the occipital region (Fig. 2A). He remained asymptomatic on treatment, and a repeat scan after 2 months showed resolution of the cyst (Fig. 2B).

**Case 3**

A 24-year-old man saw multiple, brightly colored, revolving spots of light on the right side of his visual field. They spread rapidly across the whole field. He had been having identical attacks once or twice a year for 2 years, with a marked increase in frequency within recent months. Each visual episode lasted less than 3 minutes and was followed by blurred vision for another 2 minutes. He also described a heavy sensation at the back of his head during the episodes. Systemic examination was normal. Neuro-ophthalmic examination was also normal, except that visual
### TABLE 1. Details of cases

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/ gender</th>
<th>Visual disturbance</th>
<th>Visual fields</th>
<th>Imaging</th>
<th>Scalp EEG</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18/male</td>
<td>For past 2 months, three to four 2-minute episodes of seeing revolving red, green, blue circular spots of light in right hemifield, spreading rapidly across whole field. No headache</td>
<td>Normal</td>
<td>7-mm ring-enhancing lesion with perifocal oedema in left occipital region on CT (Fig. 1A)</td>
<td>Normal</td>
<td>Albendazole 15 mg/kg, prednisolone 1 mg/kg for 28 days; carbamazepine 10 mg/kg for 3 years</td>
<td>After starting treatment, the visual hallucinations disappeared. Repeat CT after 2 months showed resolution of cyst (Fig. 1B)</td>
</tr>
<tr>
<td>2</td>
<td>20/male</td>
<td>For past 2 months, once or twice weekly 2-minute episodes of seeing a spinning, white, bright, circular spot of light with zigzag edges in right hemifield. It spread immediately across the whole field. No headache</td>
<td>Normal</td>
<td>CT showed an 8-mm left medial parieto-occipital region-enhancing lesion with perifocal edema extending to the occipital lobe (Fig. 2A)</td>
<td>Normal</td>
<td>As above</td>
<td>After starting treatment, the visual hallucinations disappeared. Follow-up CT scan after 2 months showed resolution of cyst (Fig. 2B)</td>
</tr>
<tr>
<td>3</td>
<td>24/male</td>
<td>For past 2 years, twice-yearly 2-minute episodes of seeing multiple red, green, blue revolving spots of light in right hemifield. Followed by blurring of vision and heaviness on the back side of head for another 2 to 3 minutes. For last 3 months, episodes had become more frequent</td>
<td>Right homonymous superior quadrantanopsia confined to peripheral field</td>
<td>T2 MRI showed left anterior 5 × 8 mm occipital lesion that was hypointense centrally with peripheral hypointense rim and perifocal oedema (Fig. 3A)</td>
<td>Normal</td>
<td>As above</td>
<td>Two visual episodes while on treatment. After increasing the dose of carbamazepine, episodes ceased. Six months after treatment, visual fields improved. Twelve months after treatment, MRI showed complete resolution of cyst (Fig. 3B)</td>
</tr>
<tr>
<td>4</td>
<td>28/male</td>
<td>Gave history of seeing a circular flickering light on left side of visual field for last week. Light was stationary and colorless and did not spread to the whole field. It remained for 2 minutes. He experienced such attacks twice, and they were followed by mild headache</td>
<td>Normal</td>
<td>T1 enhanced MRI showed a 5 mm ring-enhancing lesion with perifocal oedema in right anterior occipital region (Fig. 4)</td>
<td>Normal</td>
<td>As above</td>
<td>Once treated, visual episodes ceased. Patient refused follow-up imaging</td>
</tr>
</tbody>
</table>

CT, computed tomography; EEG, electroencephalography; MRI, magnetic resonance imaging.
fields showed a right homonymous superior quadrantanopia. Scalp EEG was normal. Brain MRI revealed an oval 5 × 8 mm lesion in the left anterior occipital region that was hyperintense centrally with a peripheral hypointense rim (Fig. 3A). While on treatment, he had two similar visual episodes. The carbamazepine dose was increased, and he became asymptomatic. After 6 months of treatment, visual fields had improved. A follow-up MRI after 1 year showed complete resolution of the cyst (Fig. 3B).

Case 4
A 28-year-old man reported 2-minute episodes of seeing a stationary, circular, flickering light on the left side of his visual field for the last week. It did not spread across the whole field. The visual symptoms were followed by a mild headache. He had no other complaints. Systemic and neuro-ophthalmic examination were normal, including visual fields. Scalp EEG was normal, while brain MRI showed a 5-mm ring-enhancing lesion with perilesional edema in the anterior occipital region on the right side (Fig. 4). On treatment, he did not have further visual symptoms. He refused a follow-up MRI.

DISCUSSION

Visual hallucinations associated with seizures differ from those of migraine in that they 1) are of short duration, 2) lack a fortification spectrum, 3) are typically invariant from one episode to another, 4) lack a march or build-up of the visual disturbance across the visual field, and 5) always occur in the same hemifield (contralateral to the lesion) (1,5-8). Sometimes they show similarities with migraine visual hallucinations in that they may be colored and may spread across the whole field.

We describe four patients whose only symptom was frequent episodes of seeing single or multiple, colored or white, circular spots of light that often rotated and that first appeared laterally in a hemifield and later spread across the whole field. Each episode was identical except that the duration varied from less than 2 minutes to 3 minutes. One patient had visual hallucinations with zigzag edges, but the edges were not black and white as described in migrainous hallucinations. In the study by Panayiotopoulos (6) of 50 patients with migraine and 20 patients with occipital lobe hallucinations, we found that none of the patients with lateral occipital lesions had visual field defects. Most patients with medial occipital lobe or occipital pole lesions had visual field defects, but two patients in this group showed normal visual fields.

Focal seizures are common in parenchymal neurocysticercosis. They may be motor or sensory, depending on the location of the cyst in the brain. Seizures occur during the degenerative phase of the cyst, as the death of the cysticercus releases larval antigen that can stimulate or exacerbate an inflammatory host response (13,14). By imaging criteria, our four patients had degenerating cysts with perilesional edema. This inflammatory edema is responsible for the ictal phenomenon, as live cysts are asymptomatic (13). In this study, EEG was normal in all cases. This finding suggests that scalp EEG recording is incapable of detecting such focal seizures. Williamson et al. (3) and Svennbyornsdottr (15) also observed that intracranial EEG recording was more helpful than scalp EEG recording in identifying occipital lobe seizures in their cases. This study suggests that in an endemic region like India, cysticercosis should be suspected in patients presenting with visual hallucinations, particularly if these hallucinations have distinctive clinical features such as monotonous unilaterality, brief duration, and lack of build-up phenomena.

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Oscillopsia Without Nystagmus Caused by Head Titubation in a Patient with Multiple Sclerosis

Frank A. Proudlock, PhD, Irene Gottlob, MD, and Cris S. Constantinescu, MD, PhD

Oscillopsia in patients who have brain stem disorders but not nystagmus is attributed to a failure of the vestibulo-ocular reflex (VOR) to compensate for head movements. We report a patient who had marked head titubation and oscillopsia in aggressive multiple sclerosis but no nystagmus. Her severe head titubation precluded our ability to measure a VOR accurately. Because oscillopsia has also been described after rapid voluntary head oscillations in normal subjects, we queried whether the oscillopsia in our patient could be ascribed to the head movement alone. Six normal control subjects did not experience oscillopsia while shaking their heads at the same frequency as the patient's titubation. We conclude that the oscillopsia in our patient was probably the result of an impaired VOR or an alternative compensatory mechanism.

 METHODS

Head and eye movement recordings of the patient and normal subjects were performed using a high-resolution infrared video pupil tracker (EyeLink Eye Tracker, SensoMotoric Instruments, Freiburg, Germany), which was used to sample OD and OS position at a rate of 250 Hz. The eye data were calibrated using a series of nine fixation points repeated until satisfactory values were achieved. The head position was derived from the same system using a series of four infrared markers placed around the screen, tracked with an infrared camera mounted on the forehead above the eyes. The quality of the head data was verified by pointing the head to a series of targets using a laser pen mounted on the head. Pupil and head tracking cameras were mounted on a head clamp. The whole system weighs less than 500 g and is balanced around the head horizontal rotational axis. The subject was instructed to look at a dot projected onto a screen every second. The stimulus was created by a VisualLab stimulus generator (SensoMotoric Instruments) and projected onto a rear projection screen using a XGA video projector (Hitachi CPX-958). The subject sat in a chair 1.2 m from the screen. Eye tracker recordings were converted into Spike2 neurophysiological software (Cambridge Electronic Design, UK).
FIG. 1. Magnetic resonance imaging of the brain showing multiple T2 hyperintense lesions characteristic of multiple sclerosis in the (A) hemispheric white matter, (B) brainstem, and (C) cerebellum.

In addition, a triaxial accelerometer (Model EGCS-A-2, sensitivity 2378 mV/g; Entrant, Herts, UK) of 50 g weight was mounted on the head of the control subjects to confirm the measurements of the eye and head tracker system. A 12-bit analog to digital converter (Model 1401 Micro; Cambridge Electronic Design, UK) was used to sample the head acceleration data at 1 kHz. The accelerometer was mounted independently from the eye and head tracker to test for artefacts resulting from slippage of the head clamp.

To obtain recordings with the head immobilized for the patient with head tremor, the patient's head was firmly held manually by her husband. Head movements were recorded for normal control subjects who generated voluntary head oscillations at 4 to 5 Hz while reading the Moorfields bar reading book (Clement Clark Ltd, London, UK).

RESULTS

Patient

Our 41-year-old patient was well until 9 years prior to our evaluation, when she developed the first symptoms of MS. These included paresthesiae in the hands and legs and ataxia. She subsequently had an aggressive course marked by relapsing neurologic events. The diagnosis of MS was confirmed by magnetic resonance imaging scan, which showed multiple hyperintense lesions in the periventricular white matter of both hemispheres, in the corpus callosum, and throughout the brainstem and cerebellum (Fig. 1). The course of her MS became secondarily progressive, and she developed a spastic paraparesis, bilateral hand intention tremor, head titubation, and significant oscillopsia in the absence of nystagmus.

On our initial evaluation, she reported decreased vision and oscillopsia, which she described as the illusion of seeing the environment oscillating. A 4 to 5 Hz head titubation was observed. Bilateral optic disc pallor was present. Examination of the eye movements with the head immobilized by the patient's husband failed to reveal significant nystagmus. Without head immobilization, she could not read the 6-meter visual acuity chart. With the head firmly immobilized manually by her husband, visual acuity improved to 6/36 in both eyes. Hearing was intact. The remainder of her neurologic examination was notable for appendicular and gait ataxia and a spastic paraparesis.

Head movement recordings showed 4 to 5 Hz head tremor (Fig. 2). When the head was immobilized, no nystagmus was seen. The patient reported no oscillopsia. Precise measurements of VOR gain were not possible due to technical difficulties with calibration caused by her head tremor. Also because of the head tremor, caloric testing was not practicable. Saccadic velocities were symmetrical between the two eyes and reasonably accurate (Fig. 3).

Treatment with gabapentin (4) in escalating doses up to 2700 mg daily moderately dampened the tremor and the oscillopsia, and her visual acuity increased to 6/60 without the head being stabilized.

Control Subjects

Six control subjects (two men, four women, mean age 35 years, SD 13 years, range 23–58 years) with no neurologic or ophthalmologic abnormalities (other than corrected refraction in three subjects) were investigated for the occurrence of oscillopsia during voluntary head oscillations.

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mean and standard deviations of the voluntary head oscillations generated by the control subjects were 4.8 Hz and 0.43 Hz, respectively, similar to the mean frequency of the head titubation of the patient (4.5 Hz). The amplitude range was wide, with maximal values up to four times greater than that generated by the patient. The six normal subjects did not report oscillopsia. Five subjects could read page N5 of the Moorfields bar chart (equal to visual acuity 6/5) during voluntary head shaking. In one control subject (3 diopter myopia in either eye), visual acuity decreased from N5 to N8 during high amplitude head movement (exceeding the patient’s tremor amplitude).

**DISCUSSION**

In normal subjects, head movement does not typically result in oscillopsia because an efficient VOR and possibly other compensatory mechanisms maintain visual fixation. Oscillopsia does develop in patients who have an impaired VOR in addition to head tremor (7,8). In our patient, as we presume in many patients with MS, the rapid titubation precluded our ability to accurately measure the VOR. Rapid, high amplitude head shaking may also lead to oscillopsia even in normal people (9). However, the control subjects in this study did not report oscillopsia at a degree of head shaking equivalent to our patient’s. We are left with the presumption that in our patient, the oscillopsia and the resultant reduced visual acuity were caused by a deficit in the VOR or another compensatory mechanism that we could not measure.

This case demonstrates that oscillopsia in MS can, in rare cases, be caused by head tremor in the absence of nystagmus.

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**Fig. 2.** Simultaneous eye and head movement recordings show oscillations of the head (clinically corresponding to tremor, titubation) with simultaneous oscillations of the eyes, which do not represent nystagmus. With the head stabilized manually, there is no evidence of nystagmus. Upward deflections of the recordings indicate movement to the right; downward deflections indicate movement to the left.

**Fig. 3.** Eye movement recordings show similar velocities and amplitudes of saccades of the OD and OS. Upward deflections of the recordings indicate movement to the right; downward deflections indicate movement to the left.
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Isolated Unilateral Adduction Deficit and Ptosis as the Presenting Features of Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Christina Pieh, Beatrice Rossillion, Anne C. Heritier-Barras, Michel Chofflon, Theodor Landis, and Avinoam B. Safran

A patient with chronic inflammatory demyelinating polyneuropathy (CIDP) presented with an isolated unilateral adduction deficit and ptosis. Investigations were negative until the onset of limb weakness and fatigue 2 years later. At that time, electroneuromyography, cerebrospinal fluid examination, and magnetic resonance imaging confirmed the diagnosis of CIDP. Thus, ophthalmic signs can precede extremity and bulbar signs with a long latency in CIDP.


Chronic inflammatory demyelinating polyneuropathy (CIDP) is a symmetric polyradiculoneuropathy that affects motor and sensory fibers of proximal and distal limbs. Unlike the acute onset characteristic of Guillain-Barré syndrome and its Miller-Fisher variant, the course of CIDP may evolve over weeks to years. Typical manifestations are weakness, reduced sensation, and paresthesias. Recovery is usually incomplete even years later. Predominant involvement of ocular motor nerves is rare (1-5). We report a case of CIDP that initially presented with an isolated ptosis and adduction deficit. Two years later, more characteristic clinical features appeared.

CASE REPORT

A 35-year-old man experienced sudden onset of horizontal diplopia in left gaze and ptosis of the OD. A history of infectious mononucleosis was present. Ophthalmologic examination confirmed the right upper lid ptosis and disclosed a nearly complete adduction deficit of the OD. There were no other abnormalities. Over the next 2 years, multiple neurologic examinations failed to disclose any additional abnormalities. Cranial magnetic resonance imaging (MRI) and magnetic resonance angiography were unremarkable, as were cerebrospinal examination, serum protein electro-
phoresis, immunoelectrophoresis, and several standard batteries of chemistries and hematologic tests.

At onset of general fatigue and limb weakness, the patient was referred to our clinic. Visual acuity was 20/20 in both eyes. Biomicroscopy of the anterior segment, fundus and automated visual field examinations, electoretinography, and pattern visually evoked potentials were normal. The pupils showed equal size in dim illumination, brisk symmetric light reactions, and no afferent pupillary defect. OD ptosis of 3 mm was noted. He had an exotropia of more than 40 prism diopters in left gaze due to a nearly complete deficit of adduction of the OD. Neurological examination showed normal muscle tone and strength, diminished deep tendon reflexes, and diminished vibratory sensation of the lower limbs. Pinprick sensation in the region of the first trigeminal nerve division was diminished bilaterally, but the patient did not complain about facial numbness.

Hematochemical routine parameters, serum protein electrophoresis, and immunoelectrophoresis were again normal. Epstein-Barr virus (EBV) IgG antibodies were positive. Antiganglioside antibodies (GM1b IgM, GQ1b IgG, GD1b), anticytolinkin-associated glycoprotein, and acetylcholine receptor antibodies were negative. MRI demonstrated bilateral enhancement of cranial nerves III and V (Fig. 1A). CSF showed a cytoalbuminologic dissociation with 0 red blood cells, 7 white cells per mm$^3$ (92% lymphocytes, 8% monocytes, rare plasma cells), and a protein of 90 mg/dL. Electroneuromyography showed reduced conduction velocity and desynchronization of potentials with bilateral and symmetrical sensory and motor involvement. These results led to a diagnosis of CIDP.

After treatment with oral methylprednisolone (1 mg/kg/day) and five daily infusions of high-dose intravenous human immunoglobulin (0.4 g/kg), ptosis and limb weakness improved, but the adduction deficit was unchanged (Fig. 2).

**DISCUSSION**

In this patient who fulfilled the diagnostic criteria of CIDP(6), 2 years elapsed between the appearance of ophthalmic and extremity manifestations. Ptosis and ophthalmoplegia have generally not preceded extremity signs and symptoms in CIDP by such a long interval (1–4). In a case similar to ours, transient unilateral ptosis occurred before diplopia, and upper and lower limb muscle weakness developed 6 years later (5). However, in contrast to our patient, the CSF protein level was already elevated at the onset of ophthalmic manifestations. When ocular motor manifestations occur in CIDP, they are usually symmetric (5). Interestingly, the adduction deficit was strictly unilateral in our patient, whereas MRI enhancement of the third and fifth cranial nerves was bilateral. Enhancement of cranial nerves on MRI, which has only rarely has been described in CIDP (5), evidently need not cause clinical manifestations.

The role of infectious mononucleosis in the patient’s history is unclear. The influence of lifelong persistence of EBV on the development of an autoimmune disorder is known (7). IgG anti-GQ1b gangliosides, which play a role in the pathogenesis of ophthalmoplegia in Guillain-Barré syndrome with ophthalmoplegia and in the Miller-Fisher syndrome (8), were absent in our patient, which showed that other antibodies may be involved in ocular motor palsies. Also, anti-GM1 and anti-GD1b antibodies, which have been present in other cases of CIDP with ocular involvement (1), were absent. Anticytolinkin-associated glycoprotein antibodies, which are described primarily in sensory polyneuropathy, were also negative. Cellular or humoral sensi-

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**FIG. 2.** After treatment with methylprednisolone and 5 days of high-dose intravenous immunoglobulin, a large OD adduction deficit persists.
tivity to a myelin antigen was not evident in our case, as none of the antibodies tested was elevated. The partial recovery after intravenous human immunoglobulin and corticosteroid treatment suggests a role of humoral mediators but does not clarify their nature.

REFERENCES

Fourth Nerve Palsy, Homonymous Hemianopia, and Hemisensory Deficit Caused by a Proximal Posterior Cerebral Artery Aneurysm

Jennifer K. Hall, MD, Dina A. Jacobs, MD, Tammy Movsas, MD, and Steven L. Galetta, MD

A 21-year-old man developed an ipsilateral fourth nerve palsy, contralateral hemianopia, and contralateral hemisensory deficit as manifestations of a proximal right posterior cerebral artery aneurysm. This unusual constellation of signs reflects the involvement of the structures that run in the ambient cistern. The fourth nerve palsy and homonymous hemianopia are attributed to compression by the aneurysm. The hemisensory loss is ascribed to compromise of thalamoperforate arteries emanating from a thrombosed portion of the aneurysm.


Cisterns are CSF-filled spaces with membranous borders that surround the brainstem. The ambient cistern lies dorsolateral to the midbrain. Structures contained within this cistern include the posterior cerebral artery (PCA), the anterior choroidal artery, the optic tract, and the trochlear nerve (1,2). The PCA runs through the ambient cistern, giving off thalamic perforating arteries and anterior and posterior temporal branches. The trochlear nerve emerges dorsally from the midbrain medial to the superior cerebellar peduncle and courses anteriorly through the ambient cistern. The optic tract courses posteriorly around the cerebral peduncles, through the ambient cistern, to the lateral geniculate nucleus of the thalamus, with some fibers passing to the pretectal nucleus.

We report a patient who presented with a fourth nerve palsy, contralateral hemianopia, and contralateral hemisensory deficit owing to a proximal PCA aneurysm.

CASE REPORT

In May 2000, a 21-year-old previously healthy man presented with the acute onset of left-sided numbness and a decrease in vision. During the preceding year, the patient had had constant bifrontal throbbing headaches associated with nausea. On the day prior to admission, he developed numbness of the left arm lasting for 1 hour. As the day progressed, he experienced a severe headache associated with nausea and vomiting. One hour later, he noted the onset of visual blurriness in his left visual field, left arm numbness, and intermittent vertical diplopia worse in left gaze.

The patient had no known past medical problems and was on no medications. His family history was significant for fatal cerebral aneurysms in an 18-month-old cousin and his maternal grandfather. His neurologic examination on presentation to the neurosurgery service was significant for a left homonymous hemianopsia. There was intermittent rhythmic jerking of his left arm. He had decreased sensation to light touch in his left face, arm, and leg. Brain magnetic resonance imaging revealed a partially thrombosed aneurysm originating from the proximal right PCA (Fig. 1A and B) and an acute infarct involving the right thalamus (Fig. 1C). No subarachnoid hemorrhage was present. A lumbar puncture was normal.

A cerebral angiogram (Fig. 2A) confirmed the presence of a 2-cm partially thrombosed aneurysm at the right P2/P3 segment. The aneurysm lay just distal to the takeoff of the posterior temporal artery. The right P1 segment was hypoplastic. There was a fetal origin of the right PCA, which derived from the right internal carotid artery. There was collateral filling of the right PCA from the left PCA. The patient underwent intracranial coil embolization of the PCA aneurysm with sacrifice of the parent vessel. A postembolization angiogram (Fig. 2B) demonstrated good closure of the aneurysm with preservation of the right posterior temporal artery located proximal to the aneurysm.

Neuro-ophthalmic examination performed immediately after embolization revealed 20/20 visual acuity in OU. The patient could identify only 3/10 Ishihara color plates OD and 2/10 OS but had a history of congenital color blindness. Confrontation fields revealed a mildly incongruous left homonymous hemianopia, which was later confirmed by Goldman perimetry (Fig. 3). Also present was a mild right hypertropia that increased in left gaze and on right
head tilt. Pupils reacted briskly to light bilaterally, and there was no afferent pupillary defect. Ophthalmoscopy was normal. The left homonymous hemianopia resolved within several months, as did the right hypertropia and left hemisensory deficit. The patient had a normal follow-up computerized perimetry in October 2000.

**FIG. 1.** A: Axial T2 magnetic resonance imaging (MRI) demonstrates a right posterior cerebral artery aneurysm (arrow) compressing the posterolateral aspect of the right midbrain. B: Axial gradient echo MRI reveals signal of old clotted blood in a partially thrombosed aneurysm. C: Axial FLAIR MRI demonstrates a right thalamic infarct (arrow).

**DISCUSSION**

We report a patient with a right fourth nerve palsy, left homonymous hemianopia, and left hemisensory deficit as manifestations of a proximal right PCA aneurysm. Figure 4 demonstrates the relationship of the aneurysm to the...
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FIG. 2. A: Cerebral angiogram reveals a 2-cm partially thrombosed aneurysm at the P2/P3 segment (arrow). B: Postembolization angiogram demonstrates nonfilling of the coiled aneurysm (arrow).

adjacent structures in the ambient cistern. The patient's left hemisensory deficit was due to a right thalamic infarction. Although the thalamic perforators usually branch off from the parent PCA proximal to the location of this patient's aneurysm, it is likely that the perforators were located distal to the aneurysm because of the hypoplastic P1 segment. These perforators were either compressed by the aneurysm or, more likely, occluded by partial thrombosis within the aneurysm. The intermittent rhythmic tremor of his left arm was probably caused by ischemia to the ventrolateral nucleus of the thalamus.

FIG. 3. Goldmann visual fields reveal an incongruous left homonymous hemianopia.

The right fourth nerve palsy and left incongruous homonymous hemianopia were probably caused by aneurysmal compression of adjacent pathways (Fig. 4).

Visual field loss due to optic tract lesions is unusual. In a series of 100 patients with homonymous hemianopsias, Smith (3) reported that only 3% were due to optic tract lesions. He noted that tract hemianopsias were very difficult to diagnose by perimetry. The author's clues to picking up a
tract lesion were “extreme incongruity, a negative optokinetic response, and evidence of neurologic disease in neighboring structures” (3).

Two other series have reviewed the optic tract syndrome (4,5). Savino et al. (4) documented 21 patients with lesions of the optic tract. They reiterated the importance of associated neurologic findings in identifying the optic tract as the site of the lesion (4). Without other associated neurologic findings, it would be easy to attribute a homonymous hemianopia to another location in the retrochiasmal visual pathway. Savino et al. (4) also noted that the classic tract field defect was extremely incongruous (4). The associated neurologic findings in their series included headache, change in cognition, sixth nerve palsy, hemiparesis, and paresthesias (4). None of the patients in their series had the same constellation of symptoms as our patient. Newman and Miller (5) described a series of 10 patients with optic tract lesions. They noted that an afferent pupillary defect (APD) would not be observed unless there was significant asymmetry in the degree of visual field loss between the two eyes (5). Therefore, the absence of an APD in our patient does not preclude an optic tract lesion. Their series did report one patient with an arteriovenous malformation (AVM) in the right ambient cistern who presented with a left homonymous hemianopia, left hemiparesis, and left hemisensory loss, but no fourth nerve involvement was noted. Another patient in that series with an AVM in the ambient cistern presented with a mild fourth nerve palsy. However, a hemianopia did not develop until after surgical resection of the AVM (5). Ohtsuka et al. (6) described another case of bilateral fourth nerve palsy secondary to an arachnoid cyst of the quadrigeminal cistern with extensive compression of both ambient cisterns.

The young age of our patient and the location of his aneurysm are two other noteworthy features. The incidence of intracranial aneurysms has been reported as approximately 3% in people age 20 years and younger (7). PCA aneurysms are generally uncommon (7–9), accounting for only 0.26% to 1.0% of intracranial aneurysms (9). Of these, only 13% are PCA aneurysms occurring distal to the posterior temporal branch (9). However, in the pediatric population, higher frequencies of aneurysms located in the posterior circulation have been noted (10). Meyer et al. (10) found a rate of 46% in their study of 24 aneurysms in patients aged 18 years or younger. However, large series have not substantiated this observation (10). Meyer et al. (10) also observed a male predominance among pediatric intracranial aneurysm patients.

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Ocular Motor Features of Alternating Hemiplegia of Childhood

Robert A. Egan, MD

A 14-month-old boy with alternating hemiplegia of childhood, an idiopathic disorder of early childhood causing episodic hemibody tonic spasms and hemiplegia, showed repetitive jerks of abduction of the ipsilateral eye during the spells. The mechanism of this ocular motor abnormality is unknown but may be unique to this disorder.


Alternating hemiplegia of childhood (AHC) is a rare disorder that affects children in the first year of life. They experience spells of tonic spasm or hemiplegia of varying duration that will alternately affect one side of the body and then the other. Previous descriptions of concurrent eye movement abnormalities mention monocular pendular nystagmus (1), strabismus (1), and episodic eye deviations (2). This report helps to clarify the ocular motor disorder accompanying AHC.

**CASE REPORT**

A 14-month-old boy was reported by his parents to have developed a 30-minute spell of OS abduction with posturing of the left arm at 7 days of age. The next spell occurred several days later, manifested by OD abduction and right arm posturing. The ocular motor spells subsequently alternated from one eye to the other with varying frequency. Occasionally, the boy would have several spells a day, but could be free of them for over 2 weeks. At 8 months of age, he began developing concurrent ipsilateral hemiplegia instead of tonic posturing during the spells of eye abduction. The hemiplegia was most dramatic during right eye spells. Spells aborted with sleep but otherwise lasted minutes to hours. Consciousness was unaffected, and he occasionally became hypotonic prior to spells. Flunarizine did not alter the duration or severity of spells, but he obtained some relief with high doses of phenobarbital.

He was born at 39 weeks gestation by cesarean section due to failure to progress and was hypotonic following delivery. He was not ambulatory at the time of examination (age 14 months). His interictal neuro-ophthalmologic examination at 14 months of age was normal apart from mild generalized hypotonia. Review of a videotaped spell at 18 days of age showed repetitive abducting jerks of the OS at a frequency of about 1 Hz (Fig. 1). The OD remained stationary in primary position and at times appeared to be tonically abducted a few degrees. The left arm was held in a raised and flexed position. Interspersed throughout the prolonged spell were several 3-second to 5-second bursts of very rapid upbeat nystagmus.

A second videotaped spell at 1 year of age disclosed abducting jerks of the OD at a frequency of about 1 Hz (Fig. 2A). There was no tonic deviation of the OS or upbeat nystagmus. During the period of repeated OD abduction jerks, the right arm was flaccid (Fig. 2D).

Magnetic resonance imaging of brain, computed tomography of chest and abdomen, cerebrospinal fluid, urine amino acids, and urine organic acids were normal. No mitochondrial genetic defects were identified. Electroencephalography (EEG) telemetry monitoring for 3 days revealed generalized slowing, but no spells occurred during that period.

At 2 1/2 years of age, he continues to have 10 attacks of isolated hemiplegia per month and four attacks of hemiplegia combined with monocular eye deviation and nystagmus per month, despite a prophylactic daily regimen of 5 mg flunarizine and 75 mg phenobarbital. If given promptly at attack onset, diazepam 1.5 mg orally or 2.5 mg rectally aborts the manifestations. The hemiplegia sometimes progresses to involve the opposite side of the body, leading to an asymmetric quadriplegia. Intercital periods last hours to days. He knows six sign language words and is still nonverbal and nonambulatory.
DISCUSSION

Alternating hemiplegia of childhood is characterized by paroxysmal spastic or dystonic attacks affecting one side of the body with onset prior to 4 months of age (1). Head deviations are uncommon. As the infant ages, the tonic attacks are often followed by hemiplegia. The prognosis for normal development is poor, and cognitive impairment becomes more apparent with age (3,4). Nearly all patients are developmentally delayed (5).

Hemiplegic attacks replace the tonic spasms as the predominant attack by 1 year of age. In one report (1), only one of 22 children was free of hemiplegic attacks by 1 year. Episodes of dystonic posturing may still appear within the spells of hemiplegia. Attacks last minutes to hours and may be bilateral. It is not uncommon for spells to be abolished by brief sleep. Paroxysmal autonomic phenomena, frequent early in the course of the illness, consist of focal blanching of a limb or whole side of the body (1). These autonomic phenomena often usher in the hemiplegic attacks. A family history of migraine is common.

Almost all children are hypotonic and ataxic and delayed in physical and mental development (1,3). Neuroimaging is routinely normal, and EEGs during spells rarely reveal epileptiform activity, although a number of patients later develop seizures (1,3).

In one report (1), episodic nystagmus was reported in 18 of 20 children; the nystagmus was monocular in 14, horizontal in 13, vertical in three, and not further described in the remaining two patients. The nystagmus typically alternates from eye to eye with each subsequent episode, as does the hemiplegia (1,6). Anisocoria occurs occasionally, the larger pupil contralateral to the abducting eye or gaze deviation (3,7). The nonabducting eye has been reported to have reduced horizontal but intact vertical movements during the spells. This patient demonstrated horizontal abduction jerks of one eye, but several jerks were accompanied by a tonic abducting deviation of the fellow eye. When vertical nystagmus was observed, it affected both eyes with very similar amplitudes. Apart from hypotonia, the monocular abduc tion jerks were the first manifestation noted by the parents.

The pathophysiology of the ocular motility dysfunction remains elusive. It is enticing to propose that epileptic activity from one cerebral hemisphere is responsible for tonic conjugate gaze deviations, but this proposition fails to explain the monocularity of the deviations. It seems more plausible that a pontine lesion causes the abduction jerks and inhibits the medial longitudinal fasciculus interneurons, preventing horizontal movement of the fellow eye.

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Delayed Visual Loss Following Pergolide Treatment of a Prolactinoma

Hideki Chuman, MD, PhD, Wayne T. Cornblath, MD, Jonathan D. Trobe, MD, and Stephen S. Gebarski, MD

A patient who had achieved marked improvement in vision and shrinkage of a prolactinoma following treatment with pergolide (0.1 mg/day) suffered a marked worsening of vision 7 months after continued treatment at the same dose. Brain magnetic resonance imaging (MRI) at the time of visual loss showed further shrinkage of the tumor and prolapse of the chiasm into the pituitary fossa. The dose of pergolide was cut in half (0.05 mg/day); 12 months later, vision had completely recovered. Brain MRI at the time of visual recovery showed no change in the position of the prolapsed chiasm. This is the 11th reported case of delayed visual loss following dopaminergic treatment of prolactinoma. Recovery of vision always occurs with reduction of the medication dosage. Many patients whose prolactinomas are treated in this fashion display chiasmal prolapse, and few suffer visual loss. Considering that visual recovery occurs without a visible change in the position of the chiasm, traction is an unlikely cause of delayed visual loss. Therefore, the term chiasmal traction syndrome, used to describe visual loss with prolapsed chiasm following surgical and radiation treatment of sellar tumors, should not be applied in this setting lest it prompt consideration of surgical chiasmapexy. The proper management is reduction of the dopaminergic agonist dosage. (J Neuro-Ophthalmol 2002;22: 102-106)

Pergolide (Permax; Athena Neurosciences, San Francisco, CA), a dopaminergic agonist, reduces prolactin synthesis, decreases the size of prolactinomas, and improves visual field defects resulting from chiasmal compression (1). Its more common side effects of nausea, orthostatic hypotension, nasal congestion, and depression rarely limit its use (1).

We describe a patient whose prolactinoma-induced bitemporal hemianopia disappeared with standard doses of pergolide but recurred 6 months later with continued treatment at the same pergolide dose. Cutting the pergolide dose in half reversed the visual field defect. Delayed vision loss has previously been reported in ten patients treated with bromocriptine or cabergoline (2-5). We present our case to document that this phenomenon may also occur with pergolide treatment and to emphasize that the mechanism of the delayed visual loss is unlikely to be traction on the optic chiasm.

CASE REPORT

A 64-year-old woman had a 1-year history of progressively blurred vision in the OD. She had had diabetes mellitus for 32 years and had been taking insulin for 5 years. She denied galactorrhea.

Visual acuity was 20/50 OD and 20/25 OS. There was a right afferent pupillary defect. Visual fields performed on the Humphrey Field Analyzer showed a temporal hemianopic defect in the OD and an arcuate defect in the OS (Fig. 1A). The optic discs and the rest of the neuro-ophthalmologic examination were normal. Brain magnetic resonance imaging (MRI) showed an intrasellar mass with lateral, infrasellar, and suprasellar extension severely deforming the optic chiasm (Fig. 1B).

A prolactin level was 3,894 ng/mL (normal = less than 23). She was diagnosed as having a prolactin-secreting pituitary adenoma and began taking oral pergolide 0.1 mg/day. Within several weeks, she noted a marked improvement in her vision.

Seven months after starting pergolide treatment, her prolactin level had fallen to 63 ng/mL. Visual acuity was 20/20 OU. Papillary reactions were now normal. Visual fields had nearly normalized (Fig. 2A). A brain MRI showed marked reduction in the size of the pituitary tumor with reduced deformity of the optic chiasm, which had descended into the sella turcica (Fig. 2B). She continued to take pergolide 0.1 mg/day.

Six months later (13 months after starting the pergolide treatment), she noted that the letters on the temporal side of OU visual field were missing. Visual acuity was 20/30 OD and 20/25 OS. Pupils were normal. Visual fields

Kellogg Eye Center, Departments of Ophthalmology (HC, WTC, JDT), Neurology (WTC, JDT), and Radiology (Neuroradiology) (SSG), University of Michigan Medical Center, Ann Arbor, Michigan, USA.

Address correspondence to Jonathan D. Trobe, MD, Kellogg Eye Center, 1020 Wall Street, Ann Arbor, MI 48195, USA
Our patient represents the 11th reported case of delayed visual loss after dopamine agonist treatment of prolactinoma (2–5). Taxel et al. (2) reported a similar patient whose bitemporal hemianopia resolved almost completely on bromocriptine 5.0 mg/day but returned slightly 3 months after bromocriptine treatment at 7.5 mg/day. As in our case, MRI at the time of visual loss showed further tumor shrinkage and now showed chiasmal prolapse. The bromocriptine dose was reduced to 5.0 mg/day, and within 2 months, the visual field defects had recovered, but MRI showed no change in the position of the prolapsed chiasm.

In a series of ten dopaminergic agonist-treated prolactinoma patients (4), Moster et al. (4) described one patient who was treated with bromocriptine at 15 mg/day and suffered a late decline in vision, but the authors did not mention whether the chiasm was prolapsed. Kaufman et al. (5) listed one patient as suffering delayed visual loss with chiasmal prolapse, but no details were presented.

Jones et al. (3) described seven prolactinoma patients in whom visual loss developed from 4 months to 10 years (median, 10 months) after being treated with dopaminergic agonists. All patients eventually recovered vision fully with reduction in the dopaminergic agonist dosage, but the authors provided details on only two patients, both of whom were treated with relatively high bromocriptine doses (20
mg/day and 10 mg/day). In one case, complete visual recovery occurred immediately after discontinuing the bromocriptine for 2 weeks and was maintained for 5 years at a bromocriptine dose of 5 mg/day; in the other case, complete visual recovery occurred within 3 weeks after the bromocriptine dose was lowered from 10 mg/day to 5 mg/day. The prolactin levels doubled or tripled after a reduction in the bromocriptine dose, but the patients suffered no ill effects. Although follow-up imaging was not explicitly described, the authors mentioned that at the time of visual recovery, “there was no obvious reduction in the degree of chiasmal herniation.”

Although imaging failed to show any relief in chiasmal prolapse, Taxel et al. (2) and Jones et al. (3) presumed that the reduction in dopaminergic agonist dosage caused a regrowth of tumor that was simply too small to detect radiologically but enough to release tethering of the optic chiasm or its vascular supply. Their argument is based on previously reported cases in which visual field loss developed weeks to months after surgery or radiation of sellar (usually pituitary) tumors and in which the chiasm or optic nerves were found on surgical re-exploration to be dragged down into the sella by scarred tissue (6,7) or tethered to the diaphragma sellae (8). Lysis of adhesions and packing of the sellar floor to prop the chiasm up to its normal position (chiasmapexy) has, in some cases, restored normal vision, but documentation of visual recovery is not particularly convincing (6–8).

Whereas this reasoning might apply to postsurgical or postradiation empty sella syndromes, it may not pertain to dopaminergic agonist-treated prolactinomas. First, autopsies have failed to show any evidence of sellar adhesions in such cases (5). Second, chiasmal herniation is evidently common after dopaminergic agonist treatment of prolactinomas, yet visual loss is rare. Lundin et al. (9) found chiasmal herniation in eight (80%) of ten such patients, none of whom had any visual loss.

The evidence that herniation of the chiasm is responsible for visual loss even in conditions known to cause sellar adhesions is actually quite weak. Kaufman et al. (5) found no relationship between the degree of chiasmal herniation and the severity of visual loss in seven patients with empty sella syndrome secondary to surgical or radiation treatment of pituitary adenomas. Chiasmapexy is often not successful in restoring vision and may cause visual worsening if the sella is packed too much.

Given that vision recovered completely without any restitution in the position of the optic chiasm in our patient, in the patient of Taxel et al. (2), and in the seven patients of Jones et al. (3), the notion that traction causes visual loss in
FIG. 3. Thirteen months after pergolide treatment at 0.1 mg daily. A: Visual fields show marked worsening in the defect as compared with Figure 2. B: T1-weighted coronal enhanced magnetic resonance imaging: further shrinkage of the mass with worsened distortion of the chiasm (arrow). Due to interval retraction of the mass, the chiasm is now prolapsed into the sella turcica.

FIG. 4. Six months after pergolide treatment at 0.05 mg/daily. A: Visual fields show nearly full return to normal. B: T1-weighted coronal enhanced magnetic resonance imaging shows no change in the size of the mass or the degree of chiasmal distortion and prolapse.
such cases should be questioned. An alternative possibility is that the dopaminergic agonist causes direct toxicity, vasospasm-induced ischemia, or reversible perivascular fibrosis. Although no direct neurotoxicity has been found in experimental work with dopaminergic agonists, perivascular fibrosis has been noted as a distinctive feature of surgically removed bromocriptine-treated prolactinomas as compared with prolactinomas not treated with bromocriptine (10).

The incidence of delayed visual loss following dopaminergic agonist treatment of prolactinomas is low but not negligible. In a series of eight patients treated with bromocriptine for prolactinomas, no visual loss was reported after follow-up periods of over 12 months (11). In another series of ten such patients (4), only one suffered a late decline in vision. That patient underwent a second transsphenoidal exploration, even though the chiasm was not herniated, and vision was worse after the procedure. In the series of Jones et al. (3), chiasmapexy was fortunately rejected as too risky a solution to delayed visual loss.

As applied to delayed visual loss following dopaminergic agonist treatment of a prolactinoma, the terms chiasmal traction syndrome, tethered chiasm syndrome, and chiasmal herniation syndrome should be avoided. They imply a mechanism that may be incorrect and is likely to prompt a surgical maneuver—chiasmapexy—that may worsen vision (4). If imaging fails to disclose tumor enlargement as the cause of delayed visual loss, the correct approach is to lower the dopaminergic agonist dose. Patients apparently do not suffer this complication at doses equivalent to bromocriptine 5 mg/day. Although higher doses may be necessary to normalize the prolactin level, they should be used only if the patient's endocrine status is clinically unsatisfactory. Visual acuity and visual fields should be monitored for several years after dopaminergic agonist treatment is begun, because delayed visual loss has been reported as long as 24 months later.

REFERENCES

Periodic alternating nystagmus is a rare central nervous system disorder in which the eyes undergo a horizontal jerk nystagmus that periodically reverses direction. A patient with a hypoplastic cerebellum and enlarged cisterna magna exhibited transient periodic alternating nystagmus following an attack of Ménière’s disease. We hypothesize that in susceptible individuals with cerebellar disturbances, periodic alternating nystagmus may be transiently induced by vestibular stimuli.

An enlarged cisterna magna is usually an anatomic finding unaccompanied by clinical abnormalities (1-3). Nevertheless, as it is a developmental anomaly, it may be associated with genetic disorders such as trisomy 18 (4,5) and cerebellar dysgenesis (6-10).

We report a case in which a patient with an enlarged cisterna magna and cerebellar hypoplasia exhibited transient periodic alternating nystagmus (PAN) during an attack of Ménière’s disease. PAN is a congenital or acquired central nervous system disorder in which the eyes undergo a horizontal jerk nystagmus that reverses direction about every two minutes (11). When acquired, PAN has been preceded by either loss of vision or a new brain stem disorder (12). Theoretical studies suggest that PAN in persons with cerebellar disturbances may be triggered by vestibular disturbances (13). We postulate that the transient PAN in our patient was a manifestation of the combination of a vestibular imbalance and latent cerebellar dysfunction.

Case Report
A 51-year-old Caucasian male with a history of decreased hearing in his left ear and recurrent vertigo over 10 years attributed to Ménière’s disease presented with two drop attacks. The drop attacks were not associated with headache, dizziness, vertigo, loss of consciousness, confusion, visual changes, nausea, vomiting, or chest pain, and were attributed to the “otolithic crises of Tumarkin” found in advanced Ménière’s disease (14). He was not taking any anticonvulsant medications.

His temperature was 98.7°F, respiratory rate 18, pulse 69, and blood pressure 138/77 without orthostatic variation. Neurologic examination was normal except for the following: decreased hearing in the left ear, inability to perform tandem walking, and a positive Romberg sign. While in the hospital, he developed an episode of vertigo with nausea and vomiting, during which his eyes showed strong horizontal nystagmus reported by one observer to be left-beating and by another to be right-beating.

Magnetic resonance imaging (MRI) of the brain demonstrated an enlarged cisterna magna and cerebellar hypoplasia (Fig. 1). No previous images were available for comparison.

Subsequent work-up ruled out epileptic seizures and cardiac causes of syncope. Electronystagmography confirmed an alternating right-beating and left-beating nystagmus with a periodicity of approximately 40 seconds, consistent with PAN (Fig. 2). Clinical examination with Frenzel’s goggles also documented PAN. Pursuit was normal for age. Fixation suppression was modestly impaired at low frequencies; gain was greater than 0.1 from 0.01 to 0.1 Hz during visual-vestibular interaction testing using a rotatory chair.

Following treatment with baclofen 10 mg three times daily, the nystagmus abated. On repeat examination using Frenzel’s goggles 1 month later, it was not evident. Baclofen was stopped at that point, and on a repeat examination 6 months later, PAN was again not evident.

Discussion
PAN has previously been reported in various forms. Congenital PAN is mainly found in albinism (15,16), while acquired PAN has been reported in cerebellar disorders and after visual impairment (17,18). Both congenital and acquired PAN can often be abolished by treatment with baclofen (19,20).

Address correspondence to Timothy C. Hain, MD, Associate Professor, Northwestern University Medical School, 645 North Michigan, Suite 1100, Chicago, IL 60611-3008, USA; E-mail: t-hain@northwestern.edu
Cerebellar disorders associated with PAN include arachnoid cyst of the posterior fossa (21), Arnold-Chiari malformation (22), spinocerebellar degeneration (23–26), various focal cerebellar lesions associated with multiple sclerosis (27), and cysticercosis (28). PAN can occur as a side effect of anticonvulsant medication (29), and in this case it is presumably also related to cerebellar dysfunction. There is substantial evidence that PAN can be the result of damage to the cerebellar uvula and nodulus. For example, PAN can be induced in monkeys by lesions of the nodulus (30,31). In humans, many reports of PAN are associated with diffuse cerebellar lesions, but some have been associated with small lesions of the nodulus. Kennard et al. (32) reported a case of PAN in a patient with cerebellar medulloblastoma, a tumor that arises in the cerebellar nodulus. In our case, we hypothesize that the cerebellum, including the...
nodulus or uvula or their connections, was damaged early in life, thus resulting in an enlarged cisterna magna and a tendency toward PAN.

PAN can also be associated with visual disturbances, such as cataract, and resolve when vision improves (17, 18). This suggests that PAN does not require a central lesion. Theoretical analyses of PAN postulate that it is related to loss of central inhibition of vestibular circuitry (13, 33, 34). In these models, PAN can be induced with vestibular signals. In our patient, perhaps the Ménière’s attack provided the trigger for PAN in a similar fashion.

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A patient displayed a pink mass on the right optic disc and normal visual function that was diagnosed as a capillary hemangioma. Seven months later, he developed typical features of nonarteritic anterior ischemic optic neuropathy (NAION) in that eye. Such a long latency between “preemptive” and “eruptive” disc edema has not been well documented in NAION.


A 55-year-old man with a history of hypertension was referred for evaluation of an optic nerve abnormality in the OD. A complete eye examination four years earlier was normal. At presentation, the visual acuity was 20/20 OU, and the external and afferent examinations, including color vision, pupils, and Goldmann visual fields were normal. The fundus examination OD showed a fleshy appear-

ing pink “mass” with dilated blood vessels occupying the superotemporal optic nerve (Fig. 1A). The left optic nerve was normal, as were both retinas.

A laboratory evaluation including ESR, RPR, FTA-ABS, ACE, CBC, and hemoglobin A1C level was unremarkable. An ultrasound was normal except for disc elevation. Fluorescein angiography demonstrated patchy choroidal filling in the area surrounding the optic nerve (Fig. 1B). The area occupied by the lesion showed marked capillary prominence and vascular telangiectasias. The optic nerve stained late in the area of the lesion (Fig. 1C). Based on the patient’s excellent visual acuity, chronicity of the lesion, and behavior of the lesion during fluorescein angiography, a presumptive diagnosis of capillary hemangioma was considered.

FIG. 3. Twelve-month follow-up. The right optic disc is pale; the “pink mass” has disappeared.
On follow-up visits, the patient remained asymptomatic, and the disc appearance was unchanged. Seven months later, he noticed an area of blurring and visual loss in the inferior nasal quadrant of the OD. The visual acuity was 20/20, but an afferent pupillary defect (APD) was present OD. The optic nerve showed segmental swelling and splinter hemorrhages typical of ischemic optic neuropathy (Fig. 2A). A Goldmann visual field demonstrated an inferior altitudinal defect (Fig. 2B). Fluorescein angiography showed patchy choroidal filling, subretinal hemorrhage and more marked staining of the optic nerve (Figs. 2B,C). The OS remained normal. At one-year follow-up, the patient had 20/20 vision, a persistent field defect, an APD in the OD, and superior segmental disc pallor (Fig. 3).

Premonitory swelling in nonarteritic anterior ischemic optic neuropathy (AION) is a well recognized phenomenon (1-5). Patients with this condition are seen during an asymptomatic phase in which no visual dysfunction is measured, but the optic disc is swollen. Previous reports have demonstrated premonitory swelling in patients with a history of AION in fellow eyes or in patients with previous intraocular surgery (2,3). Hayreh described four patients with classic presentations of AION in one eye and asymptomatic disc edema in the fellow eye. These eyes eventually developed typical AION over 3 to 8 months (2).

Gordon et al. (3) described two patients with asymptomatic disc edema, one with previous AION in the fellow eye, and one patient who had undergone cataract surgery. He suggested that these patients had a form of AION severe enough to disrupt axoplasmic flow, but mild enough to prevent visual acuity loss, visual field deficits, or dyschromatopsia (3).

To our knowledge, this case represents the first report of a patient with documented asymptomatic optic disc edema who progressed to typical AION without a previous history of AION in the fellow eye and without a previous history of intraocular surgery. Our patient presented with an asymptomatic, bulbous-appearing optic nerve lesion similar to a capillary hemangioma. As reported by Hayreh, this initial state presumably represents a “mild ischemia,” wherein axoplasmic flow is focally compromised, but axonal function is intact enough to preserve vision (2). Few descriptions of fluorescein angiography of patients in the premonitory swelling phase of AION have been provided. Hayreh described capillary dilation, microaneurysms, optic disc leakage, and optic disc staining during angiography (2). These angiographic features may help distinguish the early disc swelling of AION from that of optic nerve head capillary hemangioma.

REFERENCES
We describe the first reported case of the development of bilateral crocodile tears in Guillain-Barré Syndrome. This finding is an expression of axonal degeneration in the acute phase and misdirection-in-regeneration in the chronic phase.


**Case Report**

A 52-year-old male presented in May 2001 with a 2-month history of lacrimation while eating, leading to social embarrassment. On examination there was moderate bilateral facial weakness (Fig. 1). Synkinetic movements—twitching of the corner of the mouth on blinking—were observed. The height of the tear meniscus was less than 1 mm and there was no evidence of tear film instability. Bilateral lacrimation was observed only while the patient was eating (Fig. 2), confirming a diagnosis of crocodile tears. The patient declined treatment with botulinum A toxin (2).

Seven months previously, the patient had developed Guillain-Barré Syndrome, with severe generalized paralysis and respiratory muscle involvement that necessitated ventilation for a period of 4 weeks. Cranial nerve involvement with facial diplegia and oculomotor weakness was severe. Nerve conduction studies showed only one recordable compound muscle action potential from the right median nerve and abductor pollicis brevis muscle, which had a prolonged distal latency of 13 ms and a severely reduced amplitude of 400 μV. Needle EMG of the right tibialis anterior and first dorsal interosseus demonstrated fibrillations and positive sharp waves indicating acute denervation, representing either primary or secondary axonal damage. The patient was treated with plasmapheresis and corticosteroids with recovery of function, but still suffers persistent disability from residual weakness of both the quadriceps and facial muscles.
Discussion

This report presents a case of crocodile tears, evidence of aberrant regeneration, documented for the first time in Guillain-Barré Syndrome. Histologically, Guillain-Barré Syndrome is thought to be an inflammatory peripheral neuropathy, with both arms of the immune system participating in macrophage-induced demyelination (3), resulting in conduction slowing (demonstrated in this patient) and/or acute conduction block (1). In general, axons are spared except in the most severe forms, in which Wallerian degeneration may occur. This axonal involvement may be secondary to severe inflammatory infiltration, as in the most common variant of Guillain-Barré Syndrome called “acute inflammatory demyelinating polyneuropathy” (AIDP) (4); alternatively, a direct attack on axons may occur in the absence of both inflammation and/or demyelination, as in the rarer “acute motor axonal neuropathy” or “acute motor-sensory axonal neuropathy” (1). Distinguishing this form in its advanced stages from AIDP (with secondary axonal degeneration) by clinical or electrodiagnostic criteria remains difficult. In our patient, there was electrodiagnostic evidence of axonal damage as evidenced by active denervation in the limb muscles. This occurred in the presence of a compound muscle action potential from the right median nerve, which had a markedly prolonged distal latency of 13 ms (normal value < 4.3 ms) (5), evidence of severe demyelination indicating that in this case the axonal injury was most likely secondary to a severe inflammatory form of AIDP.

The facial nerve is the most commonly involved cranial nerve in Guillain-Barré syndrome, with facial diplegia occurring in more than 50% of patients (1). Axonal compression or disruption at any point along the course of the facial nerve may lead to neural misdirection caused by aberrant regeneration. Aberrant regeneration refers to the re-sprouting of axons down incorrect myelin sheaths after disruption of the nerve. The facial nerve contains fibers that are secretomotor for the submandibular and sublingual salivary glands, as well as secretory fibers to the lacrimal gland. Following severe proximal seventh nerve injury, the regenerating salivary secretomotor fibers may become misdirected and divert, via the greater superficial petrosal nerve, to innervate the lacrimal gland (6). The result is lacrimation in response to gustatory stimuli (“gustatory lacrimation”), which would normally excite a flow of saliva rather than tears (7). The term “crocodile tears” arises out of an ancient Greek myth that crocodiles tear to lure their prey and then continue to tear as they devour them (8). Unilateral cases of crocodile tears have been reported following Bell’s palsy and less often following surgery for acoustic neuroma (9) or basilar skull fracture (7); however, bilateral cases are rare (10). The bilateral nature of crocodile tears in this case is not entirely unexpected, given the essentially symmetrical involvement of the facial nerve in Guillain-Barré Syndrome.

It is surprising that this phenomenon has not been reported before. Permanent disabling weakness occurs in 5% to 10% of patients with Guillain-Barré Syndrome (3), and one would therefore have expected previous reports of incomplete recovery following facial axonopathy to be complicated by the effects of aberrant regeneration. A partial explanation may be that aberrant regeneration in polynuropathies is less well documented than regeneration in focal nerve lesions. In most polynuropathies, in contradistinction to focal nerve lesions in which the nerve is partially or completely transected, the architecture of the nerve is maintained and misrouting of axons is therefore thought less likely to occur (7). Regrowing axons are constrained to run inside the old basal lamina sheaths and are thus led automatically back to the appropriate place. However, Brown et al. (11) have shown that regrowing axons can cross endoneurial walls even though the longitudinal continuity of these sheaths has not been broken. The effect of such exchanges may be minimal, as in lesions of peripheral nerve trunks in the limbs, where neighboring fibers tend to be destined for the same muscle. However, in the case of the facial nerve, where axons destined for the salivary glands closely intermingle with axons en route to the lacrimal gland, exchanging of even a small number of endoneurial sheaths will inevitably lead to far more overt errors, manifesting in this case as crocodile tears.

Botulinum toxin type A is the present treatment of choice to manage the motor complications of aberrant regeneration of the facial nerve. Recently, various authors have also shown it to be highly effective in managing the autonomic complications, such as crocodile tears (2). Treatment with botulinum A toxin was declined by our patient.
We believe this to be the first report of neural misdirection following severe axonal degeneration of the facial nerve in a patient with the acute inflammatory demyelinating polyneuropathy variant of Guillain-Barré Syndrome. This case is unusual in that the condition is bilateral and follows a polyneuropathy known to be primarily demyelinating in nature.

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Superior Segmental Optic Nerve Hypoplasia

Valerie A. Purvin, MD

A visually asymptomatic 27-year-old man was found to have inferior altitudinal visual field defects binocularly. Ophthalmoscopy revealed superior segmental optic pallor with superior nerve fiber layer atrophy, nicely highlighted in red-free photographs. The patient's mother had insulin-dependent diabetes mellitus. Recognition of this entity is important for prognosis and for avoidance of unnecessary diagnostic studies.


Midwest Eye Institute and Indiana University Medical Center, Departments of Ophthalmology and Neurology, Indianapolis, Indiana, USA.

Address correspondence to Valerie A. Purvin, MD, Midwest Eye Institute, 201 Pennsylvania Parkway, Indianapolis, IN 46280, USA.

A 27-year-old man sought further neurologic evaluation for longstanding muscle weakness previously diagnosed as limb girdle muscular dystrophy. His mother and two siblings had the same condition. His mother also had insulin-dependent diabetes mellitus. The patient had no visual symptoms.

Neurologic examination demonstrated moderate proximal weakness and muscle atrophy. In addition, confrontation visual field testing suggested inferior visual field loss binocularly and prompted neuro-ophthalmic consultation. Neuro-ophthalmic examination demonstrated uncorrected visual acuities of 20/20 in OU with normal color vision and pupillary responses. Ophthalmoscopy disclosed superior hypoplasia of the optic discs with a partial...
double-ring sign (Fig. 1A and B). Goldmann perimetry (Fig. 2) disclosed bilateral inferior altitudinal defects.

Partial optic nerve hypoplasia in the offspring of insulin-dependent diabetic mothers was first described by Peterson and Walton in 1977 (1). The fundus and visual field findings in this syndrome were more fully characterized by Nelson et al. (2), and the term superior segmental optic hypoplasia was subsequently introduced by Kim et al. (3). While initially considered to be a rare anomaly, a study of 34 offspring of diabetic mothers by Landau et al. (4) found a prevalence of 8.8%. The condition is usually bilateral, affects females more often than males, and is unassociated with other developmental anomalies. Individuals with this condition are typically asymptomatic, with the field defect discovered during routine testing, as in our patient. This form of optic disc anomaly is occasionally seen in patients who do not have a history of maternal diabetes (5). Awareness of this distinctive fundus appearance can spare the patient the time and expense of unnecessary ancillary testing.

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FIG. 2. Goldmann perimetry shows complete absence of the inferior hemifield OU.
Diffusion-weighted magnetic resonance imaging is a specialized technique that measures the degree of diffusion of water molecules within extracellular space and between intracellular and extracellular space. Diffusion-weighted imaging signal is high (bright) when diffusion is restricted, as occurs in cytotoxic damage from ischemia, inflammation, trauma, or tumor. This technique, now available on most magnetic resonance imaging units, is especially helpful in detecting early ischemic stroke and multiple sclerosis and in differentiating arachnoid cyst from epidermoid tumor and brain abscess from neoplasm.


Diffusion-weighted imaging (DWI) is a specialized magnetic resonance imaging (MRI) technique that is particularly sensitive to the normally disorganized (random, “Brownian”) microscopic motion of water molecules (1). In the brain, signal intensity on DWI depends primarily on the ability of water molecules to move within and between the intracellular and extracellular spaces via permeable cell membranes. Thus far, DWI has been used primarily for the detection of acute cerebral infarction, which impairs water mobility. However, there are other applications in which DWI facilitates diagnostic insight.

TECHNICAL CONSIDERATIONS

The increased use of DWI arises from advances in newer MR units that allow them to perform echoplanar imaging. These units contain advanced gradients capable of very fast switching times that permit each image to be acquired in approximately one tenth of a second. As a result, a whole brain DWI series can be obtained in seconds rather than minutes. A DWI pulse sequence incorporates two additional gradient pulses compared with a conventional spin echo imaging sequence. These additional pulses allow measurement of microscopic motion of water molecules. The first gradient pulse alters the magnetization of each water molecule based on the position of the molecule. The second gradient pulse completely removes this alteration as long as the water molecule remains at its original location and does not move. However, any molecular movement over the interval when these pulses are applied will lead to incomplete restoration of the water magnetization. That is, molecular motion in the presence of the “diffusion gradient pulses” leads to a loss of MRI signal. The sensitivity to diffusional signal loss is controlled by choice of an image acquisition parameter called the “b-value.” For neuroimaging, a b-value of about 1000 sec/mm$^2$ is often used because it offers good diffusion-dependent contrast and image quality (2,3). For a given b-value, the amount of signal loss reflects molecular mobility. Greater mobility, or diffusion, yields less MRI signal. Conversely, a relatively strong MRI signal implies less stationary molecules. Figure 1 illustrates the stark signal loss in fluid tissues as the b-value is increased from zero (Fig. 1A) to 1000 sec/mm$^2$ (Fig. 1B).

Molecular motions that have no directional dependence are termed “isotropic”. For isotropic media, the specific direction of the applied diffusion gradient is of no consequence. In some tissues, however, water mobility does vary with direction. These tissues are called “anisotropic”. White matter, for example, is highly anisotropic since water mobility parallel to the white matter fiber tracts is substantially greater than perpendicular to those tracts. In anisotropic media, the direction of the applied diffusion gradient is an important consideration. Thus, by control of the diffusion gradient direction, one probes structural directionality of the imaged object (Fig. 2). In “apparent diffusion coefficient” (ADC) maps, regions that contain high water mobility, such as the ventricular cavities, show up as bright relative to regions of low water mobility, such as brain tissue. Modern clinical diffusion imaging systems provide several representations of diffusion properties to accentuate or suppress directional information by appropriate mathematical combination of several directional data sets. As shown in Figure 2, the average of diffusion maps from three orthogonal directions (ADC$_{R/L}$, ADC$_{A/P}$, and ADC$_{S}$) yields a diffusion map that, by design, does not exhibit complex fiber tract patterns. This “average” diffusion coefficient map is...
FIG. 1. The effect of changing the acquisition parameter “b value” on diffusion-weighted magnetic resonance image signal intensity. A: Diffusion-weighted magnetic resonance image with a b-value = 0 sec/mm$^2$ is similar to a T2-weighted image with high signal within the ventricles (arrow) and within a glioma (arrowhead). B: DWI with a b-value = 1000 sec/mm$^2$ shows signal loss within the ventricle (arrow). The loss of signal within the glioma (arrowhead) indicates that the glioma contains fluid.

The best single quantitative representation of diffusion in the object. The diffusion-weighted image represents the raw signal strength recorded in the presence of diffusion gradients. As such, the diffusion-weighted image exhibits high mobility areas as dark relative to water confined by tissues. Note that the relative contrast of a diffusion-weighted image is nearly reversed relative to an ADC map. The utility of the diffusion-weighted image representation is that tissues with lower restricted diffusion are depicted as bright and with greater conspicuity than on ADC maps (Fig. 3).

DWI clearly distinguishes between two types of “excess water,” or edema, in the central nervous system. Vasogenic edema, caused by incompetence of blood vessels or breakdown of blood–brain barrier, is an increase in the amount of extracellular water; it is commonly seen along white matter tracts. Cytotoxic edema implies damage to cell membranes, reflecting a failure of the sodium–potassium pump needed to exclude extracellular water from the cell (5,6). This type of edema is typically seen in regions of ischemia or infarcts. On T2-weighted images, both types of edema show up as high (bright) signal. On diffusion-weighted images, vasogenic edema appears relatively low (dark) signal intensity, whereas cytotoxic edema results in high (bright) signal intensity. Occasionally, very high signal on T2-weighted images will result in high signal on diffusion-weighted images (T2 “shine-through”). ADC maps are useful in determining whether the increased DWI signal is due to restricted diffusion or T2 shine-through effects. However, in routine clinical imaging, ADC maps are often not necessary, as this distinction can be made by simple visual inspection (4). That is, if the T2 signal is not very bright and the diffusion-weighted image is very bright, the DWI high signal likely reflects restricted diffusion.

**CLINICAL APPLICATIONS**

**Cerebral Infarction**

DWI has made its greatest contribution to the evaluation of acute cerebral infarction. DWI may demonstrate most central nervous system infarctions within minutes of clinical onset. This feature makes it a valuable tool to determine whether thrombolytic therapy should be performed.

Cytotoxic edema occurs within a few minutes of a critical decrease in cerebral blood flow. This change is picked up as high signal on DWI as early as 3 minutes after clinical symptoms occur. Most infarctions will show abnormalities within 45 minutes after onset (7). The sensitivity of DWI is said to be close to 100% if 2 hours have elapsed after a brain infarction. In general, sensitivity and specificity of DWI to cytotoxic edema is close to 95%, making it one of the most reliable noninvasive techniques.

The presence of cytotoxic edema (and thus high signal DWI) does not necessarily imply irreversible cell death. Zones of brightness on diffusion-weighted images closely correspond to hypoperfused brain, but if perfusion is reestablished, DWI abnormalities may reverse.

DWI abnormalities are maximal 24 hours after a stroke and start to resolve within 7 to 14 days thereafter (Fig. 3). However, disappearance of high DWI signal does

FIG. 2. Effect of diffusion gradient direction on signal intensity. A: Gradient direction right to left (“ADC$_{RL}$”). The fibers in the optic radiations run perpendicular to this direction and are seen as “black” (arrowhead). B: Gradient direction anteroposterior (“ADC$_{A/P}$”). Because the optic radiations run perpendicular to this direction, they now have increased signal. C: Gradient direction superoinferior (“ACS$_{S/I}$”). The fibers of the genu of the corpus callosum, which run from right to left, show signal loss (arrowhead). D: A composite of images in A, B, and C (“ADC$_{Co}$”). It has no specific gradient directionality, so the image is very homogeneous. E: The standard diffusion-weighted magnetic resonance image ("DWI$_{b=1000}$"). This is the image that is routinely interpreted.
FIG. 3. Diffusion-weighted magnetic resonance image in cerebral infarct. A: Diffusion-weighted magnetic resonance image shows high signal intensity in the left frontal lobe (arrowhead) in an acute infarct. B: The corresponding apparent diffusion coefficient map shows reduced signal intensity, which indicates restricted diffusion and confirms the presence of an acute infarct. C, D: Repeat diffusion-weighted magnetic resonance imaging in the same patient 14 days later shows loss of the signal on diffusion-weighted magnetic resonance image (C) and apparent diffusion coefficient map (D).

not imply a reversion to normal cell function. In many patients, conventional MRI will show an infarct. This phenomenon, known as “pseudonormalization,” (2) is caused by cellular necrosis, which produces below normal signal intensity on diffusion-weighted images. Infarcts result in cell and axonal loss, reactive astrogliosis (gliosis), and encephalomalacia. The encephalomalacia includes cysts that contain water whose motion is not restricted. Therefore, chronic infarcts are hypointense on diffusion-weighted images. The increased translational movement of water molecules in the encephalomalacic cysts results in increased spin dephasing and signal loss. This is similar to what is seen in arachnoid cysts (see “Arachnoid Cyst Versus Epidermoid Tumor”). On ADC maps, chronic infarctions actually appear as areas of increased diffusion, that is, high signal intensity. Chronic infarctions appear smaller on diffusion-weighted images than on fast spin echo T2-weighted images (8,9,10,11,12).

Arachnoid Cyst Versus Epidermoid Tumor

DWI is helpful in distinguishing between arachnoid cysts and epidermoid tumors (Fig. 4). These lesions may have similar features on T1 and T2 MRI weighted images and do not enhance. Differentiation between them is straightforward with DWI. Because arachnoid cysts tend to contain pulsating cerebrospinal fluid (CSF), their signal intensity is low on high b-value DWI (and high on ADC maps). By contrast, epidermoid tumors are solid masses whose water mobility is relatively low. Therefore, signal is higher on DWI and lower on ADC maps than that of the surrounding CSF.

Abscess

DWI has proved useful in the preoperative diagnosis of cerebral abscesses (13). In patients with no antecedent history, it is helpful to divide enhancing lesions into infections and tumors (14). Ring-enhancing lesions contain a
FIG. 5. Diffusion-weighted magnetic resonance imaging of moderate grade astrocytoma. 

A: Axial T2-weighted image shows a high signal mass in the left basal ganglia (arrow). 

B: Corresponding diffusion-weighted magnetic resonance image shows increased signal within the mass (arrow). From this image alone, it is unclear whether the increased signal is due to restricted diffusion or ‘T2 shine-through’ effect. 

C: The apparent diffusion coefficient map shows the mass to be heterogeneous. The central area (short arrow) has reduced signal intensity, which indicates restricted diffusion, whereas the periphery (long arrow) has high signal due to T2 “shine-through” effect.

...center that represents necrosis and/or cysts. In abscesses, the necrotic area harbors a complex matrix of proteins, inflammatory cells, cellular debris, and bacteria in high viscosity pus. The water molecules are bound to carboxyl, hydroxyl, and amino acid groups on the surface of macromolecules (15). These characteristics contribute to restricted Brownian motion and result in increased signal intensity on DWI and low signal intensity on ADC. By contrast, the necrotic center of tumors contains a less viscous material composed mostly of cellular debris, serous fluid, blood products, and relatively fewer inflammatory cells. This less complex environment allows water molecules a greater degree of translational motion than occurs in abscesses. Thus, the center of tumors is often of relatively low signal intensity on diffusion-weighted images and shows a high signal intensity ADC. In addition, the blood products, which may not be obvious on conventional magnetic resonance images, result in significant effects on diffusion-weighted images that contribute to low signal intensity. To avoid contamination of T2 shine-through when evaluating a potential abscess, review of ADC maps is helpful.

**Multiple Sclerosis**

The breakdown of the myelin sheath in acute multiple sclerosis (MS) plaques reduces the motion of the water molecules in the extracellular space. Because anisotropy is relatively reduced due to the loss of organization of the white matter fibers, there will be an increase in signal intensity on DWI and a lowering on ADC (1). DWI may measure improvement in molecular motion as a response to therapy before signal changes reverse on conventional T2W or FLAIR images. DWI may also be helpful in dating MS plaques as with old infarctions, chronic MS plaques show low signal intensity in DWI and high signal on ADC.

**Primary Brain Tumor**

DWI and ADC values have the potential to differentiate the components of a tumor and assess overall cellular integrity (Fig. 5). Studies (16-18) have shown that ADC values are generally low in solid/cellular tumors relative to necrotic/cystic tumors. These observations have also lead investigators to apply ADC maps to quantify therapy-induced necrosis. The use of DWI as an indicator of therapy response has been validated with animal models and in preliminary human studies (19-21).
Topic I. Giant Cell Arteritis Revisited

Asker: I recently examined an 88-year-old woman who had developed sudden painless loss of vision in her OD. She denied symptoms of giant cell arteritis (GCA). Visual acuity was OD 20/200, OS 20/50. The OS had had a stable old optic neuropathy of unknown cause. She could not cooperate well for visual fields. There was a relative afferent pupillary defect (RAPD) OS (not OD). The right optic disc looked minimally pale (she was aphakic OD), the left disc was very pale (she was phakic OS). She had been treated with prednisone 30 mg/d for 15 days for optic neuritis. Her erythrocyte sedimentation rate (ESR) had been 65 prior to the initiation of treatment.

Temporal artery biopsy (TAB) done two days later showed intimal hyperplasia, elastic membrane disruption, but no inflammation. The pathologist said both changes could be normal in a patient of this advanced age.

I tapered her down to 5 mg prednisone/d and 2 months later, her visual acuity was 20/40 OD and 20/50 OS. I saw her this week (after 8 months of treatment), and she had a nerve fiber layer (NFL) hemorrhage off the disc margin without swelling. Otherwise she was unchanged, with an ESR of 61 and C-reactive protein (CRP) of 1.2 [normal range 0–0.8].

What would you do next?

Responder 1: In my opinion, the biopsy is positive for GCA. You may want to look at it yourself and see if the internal elastic membrane looks like mice have been chewing on it. If this is the case, then she has GCA, and her steroid dose is too low (especially with the still elevated ESR and CRP). On the other hand, such good visual recovery is against arteritic disease. Still, I would still be very nervous about GCA. You may want to biopsy the other side, but you will probably get the same report.

Responder 2: If the biopsy was of adequate size and bilaterally negative as read by a reliable pathologist, then I think it would be hard to call this GCA.

Responder 3: This sounds more like a steroid-responsive optic neuropathy than GCA. I've never seen or heard of GCA recovering from an acuity of 20/200 to 20/40. By the way, I note that the prednisone dose was given every other day. In my experience, this does not work well for optic nerve disease. I probably would not rebiopsy her, but would give her a burst of IV steroids and then restart a slow taper from 10 mg prednisone every day, while following her vision and fundus exam.

Responder 4: Going from 20/200 visual acuity to 20/40 can happen in GCA. It happens if one catches the phase of choroidal ischemia before disc infarction. If one blasts with steroids at that stage, one can induce reversal of the visual loss. I have had a few such cases, including one that went from about CF to 20/25 acuity.

Responder 3: Responder 4, I assume you mean elderly patients with poor vision, no optic disc changes, small if any RAPD, positive GCA review of systems (ROS), abnormal fluorescein angiogram (FA) and positive TAB? I have to admit I have not seen such a case yet. Are there fundus changes or other diagnostic clues to help?

Responder 4: Sometimes there are lobular choroidal changes. This may be quite subtle. A fluorescein angiogram with very early views to assess perfusion time of the choroid nails it. Here is one of the original reports of this:

**Choroidal nonperfusion in giant cell arteritis.**


**Abstract:** A 68-year-old man had visual loss secondary to isolated choroidal nonperfusion as a clinical manifestation of giant cell arteritis. Ophthalmoscopy disclosed scattered yellow-white lesions at the level of the retinal pigment epithelium in the posterior pole of the OD. Intravenous fluorescein angiography demonstrated marked delay in choroidal filling of the macula in the OD. There was no ophthalmoscopic or angiographic evidence of anterior ischemic optic...
neuropathy or central retinal artery occlusion. After approximately 72 hours of intravenous corticosteroid therapy, the patient's visual acuity improved and repeat intravenous fluorescein angiography showed normal choroidal circulation. Isolated choroidal ischemia is a potential cause of reversible visual loss in patients with giant cell arteritis.

Responder 5: I agree with Responder 4 that vision can improve dramatically in some cases when caught on time. I had two biopsy-positive patients with anterior ischemic optic neuropathy (AION) who presented very soon after the loss of vision. ESR was 120 and 100. Treatment with steroids was started immediately. One improved from LP to 20/25 and another from CF to 20/20! I have never seen this kind of response in nonarteritic anterior ischemic optic neuropathy (NAION).

Responder 6: I have two GCA patients with dramatic improvement in acuity with immediate high-dose IV steroids. One had a swollen nerve.

Responder 7: Has anyone seen biopsy-proven GCA cause AION with visual acuity of 20/30 or better?

Comment: This thread raises many issues concerning the diagnosis and management of GCA. The first issue is the diagnosis of GCA in patients on corticosteroids. This patient’s biopsy was done after 17 days of prednisone treatment and showed disruption of the internal elastic lamina, but no inflammation. This is similar to a study by Lie et al. (1) that showed a decrease in inflammatory response the longer the patient was on prednisone. We do not have the pathology report available, but presumably the pathologist commented on the differential diagnosis of disruption of the internal elastic lamina, which includes “healed arteritis.” Responder 2 raises the issue of the role for bilateral biopsy. Most series (2,3) show that biopsy of the second side produces 3% more positive results, but there are still some cases diagnosed on clinical criteria with negative biopsies (2). Another responder questions whether dramatic visual recovery occurs in GCA. Two responders share their experience of dramatic visual recovery if GCA is treated at the pre-AION stage of choroidal ischemia, which can be demonstrated on fluorescein angiography. This is in contrast to most series in which little if any improvement in vision occurs despite treatment (4–6). But perhaps the dictum that marked improvement in vision implies a disease other than GCA is incorrect. Responder 7 asks if minimal visual involvement can occur with GCA. Someone could have referred to the series of Hayreh et al. in which 26% of eyes with arteritic AION had acuity of 20/40 or better (7). Two interesting comments about treatment are ignored. Should a persistently elevated ESR and CRP prompt a change in treatment? No one answers this one, but the treatment of elevated laboratory tests without clinical changes is not clearly needed (8). Responder 3 notes that alternate day corticosteroid therapy is not effective for GCA. Comparison of alternate day and daily corticosteroid treatment shows the superior effectiveness of daily treatment (9).

II. Monitoring For Ethambutol

Optic Nerve Toxicity

Asker: What would this group consider the standard of care for monitoring visual function in patients taking ethambutol?

Responder 1: Color testing is the most sensitive test, and some advocate Farnsworth-Munsell 100 hue testing. Automated perimetry is probably second, and visual acuity is third. But the simpler test is to calculate the medication dosage in mg/kg. At doses below 15 mg/kg, toxicity is virtually unheard of. The risk increases as the dose increases.

Responder 2: Initial screening should include color plates, to be repeated at 3 months, 6 months, and 1 year after the onset of treatment. Any changes in vision should be reported to the treating physician. If these changes are thought to be due to ethambutol, the drug should be replaced with an alternative. If symptoms are caught early, visual loss can be reversed.

Responder 3: I think all that needs to be done is to warn the patient and describe the symptoms of toxicity. I have never seen toxicity be asymptomatic. The patient will be the first to know. Unless patients are not very observant, they can monitor themselves.

Responder 4: I do an examination with visual fields every 3 months and am now including Heidelberg retinal tomography (HRT) every 6 months. I include the HRT more for curiosity, to see what HRT will be able to detect if toxicity does occur.

Responder 5: Ethambutol targets the papillomacular bundle, so I monitor color vision, contrast sensitivity (looking for exclusively high spatial frequency losses), and the red-on-black Amsler grid.

For research purposes, our three-dimensional Threshold Amsler Computer System works too well: The majority of patients on ethambutol have a defect. For more on that you can go to Fink’s website: http://www.wfbabcom5.com/wG35.htm.

Responder 6: The Medical Protection Society (UK) in its 1984 report states, “It is wise to make a record of
Ocular toxicity from ethambutol.
Citrin KM, Thomas GO.

Ethambutol-induced ocular toxicity revisited.
Alvarez KJ, Krop LC.

One of the guidelines states, “routine visual acuity tests during treatment are NOT recommended.” The paper suggested, “routine tests of color vision and of peripheral and central fields might be more sensitive than visual acuity.”

In our clinics, where tuberculosis is a major problem, we usually do baseline a complete neuro-ophthalmic examination (acuity, color, and visual fields) on the first visit and repeat these exams every 1-3 months, depending on the occurrence of symptoms, while the patient is on treatment.

Concerning the comment on risk of toxicity within standard dose ranges (15 to 25 mg/kg/day), several studies have shown that toxicity can occur while patients are on so-called “safe doses”. Please check out the following references:

Toxic ocular effects of ethambutol.
Kahana LM.

Optic neuropathy associated with ethambutol in Koreans.
Choi SY, Hwang JM.

Ocular toxicity following ethambutol in standard dosage.
Chatterjee VKK, Buchanan DR, Friedmann AI, et al.

Toxic optic neuropathy secondary to ethambutol.
Inocencio FP, Castillo TR.

The literature is divided on the issue of reversibility of toxicity. Some authors claim that it is when treatment is discontinued, while others say that it is not. In our experience, recovery is not very encouraging.

Responder 7: In Istanbul, where tuberculosis is also an important health threatening disease, data on recovery after stopping ethambutol are encouraging. More than 90% of the patients get their vision back after cessation of the drug. More than 90% of the patients get their vision back after cessation of the drug.

Comment: In this thread, there is considerable disagreement about the appropriate way to monitor for ethambutol optic nerve toxicity. The asker asks what tests and testing intervals are appropriate for monitoring patients. The first two responders suggest color vision testing and a 3-month interval for testing. While some believe that Farnsworth Munsell 100 Hue abnormalities are the earliest sign of ethambutol toxicity, others believe that contrast sensitivity or visual evoked potentials are better tests for early detection of toxicity (10-12). Interestingly, there are no studies comparing the various types of color vision testing, automated perimetry, contrast sensitivity, or evoked potentials to determine which test would be most sensitive. The next responder recommends having the patient monitor vision and return only when there are difficulties. In America’s litigious climate, this approach is likely to be exceptional, but there is scientific support for it. Citron (13) notes “in my opinion routine visual acuity tests during ethambutol treatment serve no useful purpose since it appears that they fail to detect ocular toxicity before symptoms occur and may not be abnormal even when symptoms are present.” Of course, Citron’s comment refers to acuity testing, and while the best test for early detection is not yet clear, most would agree that acuity testing is much less sensitive than other modalities. The next responder mentions red-on-black Amsler grid testing and three-dimensional Amsler grid testing, two methods for testing vision that have not been formally assessed in this setting. Responder 6 notes a number of published recommendations on follow-up and mentions the practice in one clinic. Responder 1 was obviously not aware of the references from 1986, which show a 1% incidence of optic neuropathy at an ethambutol dose of 15 mg/kg (14). Not mentioned in the interchange is that ethambutol is excreted via the kidneys, and decreased kidney function can increase toxicity; ethambutol blood levels are available to help monitor dosage. Responders are divided on the issue of recovery from ethambutol toxicity. Two reputable series note 40-50% improvement (15,16).

III. Oscillopsia in Congenital Nystagmus

Ask: A 46-year-old healthy female had nystagmus noted in infancy and was told by a pediatric ophthalmologist that a "lesion in the brain caused the nystagmus." She has a null point/zone in right gaze and no oscillopsia. In her 30s, she began having occasional oscillopsia during stress, but was able to overcome it with certain maneuvers. Gradually since her 40s, she has daily oscillopsia with moments free of it, especially when performing near tasks. It improves if she closes one eye. The null point/zone has shifted to up and right gaze.
Visual acuity is 20/20 OU, with horizontal pendular nystagmus (appears like it might be jerk when very fast, but too fast for me to be sure). The nystagmus is variable in amplitude and frequency, and does seem to stop for a few moments here and there. It is horizontal in all positions of gaze. When it does stop, she sees double in the distance. During nystagmus, there is no diplopia.

So I have four questions:

1) How common is it to develop oscillopsia later in life with congenital nystagmus (CN)?
2) Should she be worked up?
3) Any positive experience with medications?
4) Which treatment modality would you try first, medications or prisms?

Responder 1: See:

Onset of oscillopsia after visual maturation in patients with congenital nystagmus.
Hertle RW, FitzGibbon EJ, Avallone JM, Cheeseman E, Tsilou EK.

Responder 2: She needs a scan. A paraneoplastic etiology is a consideration.

Responder 3: Acquired oscillopsia does occur in CN (19,22), and is related to worsening of foveation period in the nystagmus cycle. You could look at the nystagmus waveform with recordings to substantiate the diagnosis of CN. Try to see if prisms for null position and/or convergence help. Baclofen, clonazepam, and gabapentin have been only marginally helpful.

Asker: I’m still unclear what the group’s consensus is on my patient with congenital nystagmus and adult-onset oscillopsia. I read the recent article in Ophthalmology (21) regarding the five or so patients. Only one patient was imaged. Should I start with eye movement recordings to see if the pattern is consistent with congenital nystagmus? If so, would you still image? Or should she be imaged regardless?

Responder 4: I have seen several patients who have CN or periodic alternating nystagmus (PAN) recognized since childhood with adolescent or adult onset oscillopsia. All had eye movement recordings. Many have been imaged (all normal) and have had normal vestibular tests, too. Recordings were all done by Larry Abel. He then started asking all patients with CN who were sent to him to record if they ever experienced oscillopsia, and several of the first patients asked reported that they had experienced it! Oscillopsia has also been reported with latent/manifest latent nystagmus (I have seen one of these).

So:

1. Oscillopsia in CN/PAN is probably not rare—the frequency may reflect the eagerness with which it is sought as a symptom.
2. I think that a “classical” CN/PAN recording is very reassuring and should be done. CN really is a laboratory diagnosis ["the eye is quicker than the eye" (Abel LA, Personal communication)].
3. Vestibular pathology can also happen in CN patients and these patients should probably be imaged.

Comment: The absence of oscillopsia in most patients with CN is a remarkable phenomenon. These patients are usually unaware of ongoing retinal image slip occurring with velocities that patients with acquired nystagmus would find very uncomfortable (4 degrees or more). Several hypotheses have been advanced to explain why this is so. There is some evidence of decreased motion perception in CN patients (17). Other proposals include use of an efference copy of the CN waveform to negate the retinal slip effects and the suppression of visual sensation except during “foveation periods” wherein the retinal slip velocity is below a critical velocity (< 4–10 degrees/sec) (18).

The occurrence of oscillopsia in CN patients at some point after maturation of the visual system is rare, but well documented (19,20,21,22). Intercurrent phenomena that interfere with the mechanisms that usually suppress the perception of retinal slip have been postulated as causes of the onset of oscillopsia. The comment of Responder 3 alludes to the report by Dell’Osso (22) of a patient who had reversal of the predominant direction of his jerk CN and onset of oscillopsia after an episode of loss of consciousness. While the patient had previously shown well defined foveation periods with low retinal slip velocity, his new nystagmus waveform produced consistently higher retinal slip. Another patient had a Chiari malformation with onset of oscillopsia following lumbar puncture, together with a changed pattern of nystagmus: horizontal/torsional with the exponentially increasing slow phase slopes usually characteristic of CN (20).

The patients reported by Hertle et al. (21) as mentioned by Responder 1, appear to have at least two other mechanisms for new onset of oscillopsia. One hypothesis is discussed by Retinecke (23) in his commentary on their paper. This is the increased slow phase velocity of nystagmus produced by the conversion from true latent nystagmus to manifest latent nystagmus that may follow an acquired change in ocular alignment, or visual sensory function. Three of the five patients in the series of Hertle et al. (21) had a latent nystagmus component on exam. The change in ocular motility could be a decompensation of a long-standing deviation or an acquired strabismus component. Worsening of a chronic visual afferent system disorder such as a
forms of CN are readily treated (baclofen for PAN). Con­
served facial myokymia. Clinicians are often presented with
therapy fairly dramatically.

nystagmus.

mal except for some myokymic movements of the eyelids.

very extensive work-up including normal MRI/MRA.

has increasingly noticed blurred, "rolling" (vertically) vi­

healthy man on no medications who, for the past 3 years,

sponder 3, may also be attempted, although only a few
forms of CN are readily treated (baclofen for PAN). Con­
tact lenses have been reported to suppress the oscillopsia
(19).

IV. Exercise-induced Downbeat Nystagmus

Asker: I'd appreciate any thoughts on a 37-year-old healthy man on no medications who, for the past 3 years, has increasingly noticed blurred, "rolling" (vertically) vision on physical exertion or when stressed. He has had a very extensive work-up including normal MRI/MRA. When I first saw him I could find absolutely nothing abnormal except for some myokymic movements of the eyelids. I asked him to return and walk around the parking lot for a couple of hours to precipitate the symptoms. He has presented with and now presents with a dramatic downbeat nystagmus.

Responder 1: I believe your patient may have episodic ataxia type 2 (EA2). I had an identical young patient with symptoms induced by vigorous walking around downtown Seattle. Afterwards, I observed downbeat nystagmus in the examination chair, whereas the previous examination without the exercise was normal. It responded to acetazolamide therapy fairly dramatically.

Comment: This fascinating patient presents a diagnostic challenge. The Asker notes that his patient has downbeat nystagmus triggered by exertion or stress, and also observed facial myokymia. Clinicians are often presented with patients who have combinations of clinical phenomena that can be described, but not readily attributed to a single disease process known to the examiner. One way to approach such a patient is to review the literature concerning the distinctive aspects of the case and look for references to the other phenomena as a way of recognizing and establishing a potentially unifying diagnosis. This is a very time-consuming and inefficient use of the busy clinician's time, however. Fortunately, a new suite of clinical database tools has become available to make this process much more efficient and powerful.

Genetically determined diseases are frequent in neuro-ophthalmologic practice, and must be considered as one cause of the phenomena in the Asker's case. Apparently other categories of disease have been sought extensively, and are not apparent. Whenever a genetic disease is considered as a cause of a clinical syndrome, it may be very useful to visit the Online Mendelian Inheritance in Man (OMIM) Web site (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM) and query the OMIM database with the patient's findings (24). This database contains detailed genetic, molecular, and clinical information on 13434 entities as of March 16, 2002. Of these, 9958 have a known gene locus. If the OMIM database is queried with "nystagmus" and "myokymia," only six disorders are returned that include these features together in the clinical descriptions of affected kindreds. They are: episodic ataxia type 1, episodic ataxia type 2, Machado Joseph disease (spinocerebellar atrophy type 3, sca3), episodic ataxia type 4, episodic ataxia type 3, and progressive external ophthalmoplegia, and scoliosis.

Responder 1 suggests the patient in question may have episodic ataxia type 2 (EA2) and suggests a trial of acetazolamide therapy. Reviewing the OMIM article on EA2, we find that myokymia is much less frequent in EA2 than EA1 (25). From the associated literature reference links in OMIM, we can review the abstracts of the underlying citations. The two disorders are both autosomal dominant, but EA2 is a genetic defect in the calcium ion channel gene CACNA1A mapped to gene locus 19p13, and affected with the defects in the same gene that cause either spinocerebellar ataxia type 6 or familial hemiplegic migraine type 1 (25). EA2 is not associated with interictal myokymia. EA1 is caused by a genetic defect in the potassium ion channel gene KCNA1 at gene locus 12pl3. EA1 is much more likely to be triggered by body movements and is associated with interictal myokymia, including the facial muscles. However, nystagmus is not seen interictally in EA1. SCA3 is a multisystem disorder with upper motor neuron signs, extrapyramidal features, and many other aspects not seen in this patient. Episodic ataxia type 4 (EA4) is not yet mapped to a specific gene locus, and is clinically similar to EA1 with myokymia and the additional features of tinnitus and vertigo. Episodic ataxia type 3 (EA3) is not mapped, and not associated with myokymia. The description of the disorder...
called Progressive External ophthalmoplegia and scoliosis is clearly different from that of our patient. In the final analysis, this patient probably has EA2 with benign eyelid fasciculations masquerading as myokymia. Acetazolamide may help patients with EA2, EA4, and less often EA1. Phenytin may benefit patients with EA1 (26).

To identify a source of genetic testing for a patient with suspected EA2, we might subscribe to the GeneTests/GeneClinics Web site at: http://www.genetests.org/ (27). The effective use of the online database resources can give us precise direction for further evaluation of the patient and suggestions for effective therapy.

REFERENCES

27. GeneTests/GeneClinics. University of Washington School of Medicine, Children's Hospital Regional Medical Center (Seattle, WA), 2002. Available at: http://www.genetests.org/
The 27th International Stroke Conference
San Antonio, Texas, February 7–9, 2002

The 27th International Stroke Conference was held in San Antonio, Texas from February 7–9, 2002. The covered topics included epidemiology, prevention, acute treatment, outcomes, and rehabilitation, but the emphasis was on acute stroke intervention and neuroprotection. There were 18 special symposia, 15 sessions of platform presentations focused on various issues in stroke, and two poster sessions: one on basic research and one on clinical research. An anticipated special symposium on the results of the International Study of Unruptured Intracranial Aneurysms was canceled. Abstracts for the platform presentations and posters are published in *Stroke* (2002;33:342–420). Abstracts of oral presentations are referenced by number and page number (OA #, p #), and abstracts of posters are referenced by number and page number (P #, p #). The symposia were not accompanied by published abstracts.

**Warfarin and Aspirin Prophylaxis of Stroke**

The most practical information included data from studies of warfarin and aspirin in preventing stroke. Patients with cerebrovascular stenoses are sometimes placed on warfarin after antiplatelet agents fail to prevent symptomatic episodes, although limited research exists to support such treatment. Others advocate warfarin to prevent stroke in patients with antiphospholipid antibody syndrome. The Warfarin-Aspirin Recurrent Stroke Study (WARSS), the results of which were published in November 2001 (1), enrolled 2206 patients with ischemic stroke not attributable to cardioembolic stroke as the sole setting in which warfarin is proven to be more effective than antiplatelet agents. This is the most definitive study to date, although it was not powered to evaluate efficacy in specific stroke subtypes, such as those due to vertebrobasilar intracranial stenosis.

The Antiphospholipid Antibody Stroke Study (APASS) examined the role of antiphospholipid antibodies (aPL) in stroke (2,3). The initial studies demonstrated that anticardiolipin antibodies (aCL) are an independent risk factor for stroke, but that the presence of aCL positivity at the time of an initial stroke did not confer a significantly increased risk for subsequent thromboembolic events or death. WARSS and APASS researchers collaborated to determine whether there was a difference in the effect of aspirin and warfarin on recurrent stroke in patients with aPL. Of 2206 patients enrolled in WARSS, 1954 were eligible for APASS, and 1770 were enrolled in the second study. Patients were observed for the primary endpoints of recurrent ischemic stroke, death, transient ischemic attack, myocardial infarction, and pulmonary embolism. There was no difference in event rates in aPL-positive versus aPL-negative groups, regardless of treatment with warfarin or aspirin. There was also no difference in time to recurrent event in any treatment or aPL group. Average INR among patients treated with warfarin was 1.9, which may not be sufficient to have an impact or recurrent stroke in patients with aPL.

The APASS and WARSS groups collaborated to study subtypes of antiphospholipid antibodies in the cohort (P153). The lupus anticoagulant (LA) and aCL are currently used to diagnose patients with aPL. Stored serum samples from 200 randomly selected WARSS/APASS patients were tested for LA and aCL and for two more recently available aPL antibodies, anti-β2-glycoprotein-1 (β2GPI) and antiphosphatidylyserine antibodies (APS). They found that 29% of patients negative for LA/aCL were positive for either β2GPI or APS, confirming the heterogeneous nature of...
Endovascular Intervention in Cerebrovascular Disease

Carotid angioplasty with stenting is a proposed alternative therapy to carotid endarterectomy (CEA) to prevent stroke. Appropriate selection of patients for these procedures continues to be important. Two papers investigated the relationship between carotid plaque characteristics, symptoms, and complications of therapy.

Degree of stenosis has been the variable used to determine need for intervention in clinical trials of CEA, without regard to plaque morphology. Authors interested in widening the safety margin of CEA argue that unstable plaques have a higher stroke risk. Aburahma et al. (OA #6, p 343) evaluated 2460 patients undergoing carotid ultrasonography over 1 year, reviewing plaque heterogeneity, severity of stenosis, and underlying symptoms. Increasing stenosis correlated with heterogeneous plaque characteristics (Table 1). As the degree of stenosis increased, the percentage of heterogeneous plaques also increased. Furthermore, heterogeneous plaques were more often symptomatic at all degrees of stenosis (Table 2).

Carotid angioplasty and stenting remodel an atherosclerotic plaque instead of removing it. Plaque composition may play an even more important role in endovascular procedures than in CEA. Biasi reported the correlation of carotid plaque composition and complications in patients undergoing carotid stenting in the Imaging in Carotid Angioplasty and Risk Of Stroke (ICAROS) study (OA 5, p 342). Plaque composition was graded from 0 (very soft, nonhomogeneous plaque) to 100 (hard, homogeneous plaque). ICAROS studied 387 patients undergoing carotid stenting at 19 centers worldwide. There were 24 complications (6.2%): 12 transient ischemic attacks, 7 minor strokes, and 5 major strokes. Plaque characteristics correlated with complications. Nineteen of 24 complications occurred in patients with plaques graded 0 to 25, and the remaining 5 complications occurred in cases with plaques graded 25 to 50. About half of the procedures used a debris capture device, and 70% of the complications, including 4 of 5 major strokes, occurred in association with procedures performed without a debris capture device.

Cardiologists have taken the initiative in endovascular therapy for carotid stenosis at many institutions. Physicians who are not yet ready to accept this technology without demonstrated efficacy and safety from randomized clinical trials will be interested in a paper by Malisch et al., "When Is carotid stenting really necessary? Results of a conservative algorithm" (OA 35, p 348). Among 39 patients evaluated prior to carotid stenting, 25 with atherosclerotic disease and 14 with dissections or fibromuscular dysplasia, endovascular intervention was thought to be indicated in only 12, seven of whom underwent stenting in addition to angioplasty. Five had surgery, 20 were treated medically, and three required no therapy. During a mean follow-up of 19 months, there were no strokes in either treated or untreated groups. Two randomized trials examining the role of angioplasty and stenting in carotid stenosis are underway.

Carotid stenting may be performed safely, but it is not clear that the procedure is safer than CEA in patients with carotid stenosis, including those for whom referral for stenting is made because of a perceived high surgical risk. Long-term efficacy compared with CEA remains unknown. One problem in undertaking controlled trials comparing endovascular therapy with CEA would seem to be the rapid evolution in the technology of endovascular therapy. Today's best technology is likely to be supplanted with better technology by the time a study has been approved.

Special symposia on management of extracranial and intracranial stenosis concentrated on endovascular interventions. These invoked as sense of awe, as interventionalists demonstrated dramatic rescues from apparently irrevocable deterioration by intraarterial tPA and stenting procedures in patients with evolving stroke already treated with maxi-

| TABLE 1. The proportion of cases with heterogeneous plaques at increasing degrees of stenosis |
|---|---|---|
| Degree of stenosis | Heterogeneous plaques | |
| <50% | 16% | |
| 50 to <60% | 34% | |
| 60 to <70% | 62% | |
| 70% or more | 81% | |

Data adapted from OA #6, p 343

| TABLE 2. The proportion of heterogeneous versus homogeneous plaques in patients with symptoms at various degrees of stenosis |
|---|---|---|
| Degree of stenosis | Symptomatic heterogeneous plaques | Symptomatic homogeneous plaques |
| <50% | 68% | 16% |
| 50 to <60% | 76% | 21% |
| 60 to <70% | 79% | 23% |
| 70% or more | 86% | 34% |

Data adapted from OA #6, p 343
mum systemic antithrombotic therapy. As with stenting and CEA, the benefit of this focused therapy compared with systemic thrombolysis in acute stroke remains unproven. A symposium on the management of heart ischemia showed why neurologists are still behind cardiologists in intervention for stroke or threatened stroke. Cardiologists are using third generation thrombolytics, whereas neurologists are still using tPA alone. However, many of the newer agents used for cardiac ischemia have failed preliminary safety studies for acute stroke, largely because of increased rates of intracranial hemorrhage. Adjunctive therapy with antifi-
nogen agents (such as GPIIb/IIIa-receptor antagonists) to prevent rethrombosis, and repeated arterial endovascular procedures based on a variety of clinical, electrocardiogram, and laboratory parameters are used in patients with coronary artery ischemia, while no similar parameters for moment-to-moment change are available for use in patients with acute cerebrovascular ischemia.

Neuroprotection
Myron Ginsberg, MD, PhD was honored as the Willis Lecturer and brought a life's work using animal models for basic research in acute stroke treatment to the podium. He ended his discussion, "Brain Ischemia: Adventures in Pathophysiology." He focused his lecture on the utility and applicability of studying the pathophysiology of brain ischemia using small animal models of human disease, and the challenges of neuroprotective therapy. Animal models allow replicability, reproducibility, and genomic modulation—concepts often inaccessible in human subject research. Dr. Ginsberg’s research has examined local cerebral blood flow in brain ischemia, particularly as it identifies the ischemic penumbra and its associated metabolic changes in animals, and how flow gradients in ischemia determine gene expression. He stated that his work in neuroprotection has been a natural outgrowth of his cerebral blood flow research. In addressing the question, "Why have neuroprotective agents in humans failed?" he commented that human studies have often been unable to replicate the conditions that are efficacious in the laboratory, including critical treatment variables such as timing and medication doses. In addition, he mentioned that a few human studies have been conducted using agents with only a modestly protective effect in animals. He ended the lecture by emphasizing the need for a multidisciplinary approach in cerebrovascular basic science and clinical research.

Basic science posters and platform presentations also discussed the use of neuroprotective agents in animal models. Neuroprotection studies examined a variety of agents, from those commonly available in the home to viral vector gene transfers and factors influencing the success of these novel procedures.

Ethanol plus caffeine ("Caffeinol") had a neuroprotective effect in rats at doses equivalent to 3 cups of coffee and 1–2 cocktails in humans, but chronic use of alcohol reduced this benefit. A controlled clinical trial was suggested. Interferon-B and dexamethasone at a dose of 20 mg/kg were beneficial to rats with stroke. Novel agents continue to have benefit in rat models and include IL10 gene transfer and other gene transfer models, SL327 (MEK1 protein kinase inhibitor), and nitric oxide donors.

Several neuroprotection human studies and meta-

analyses were reported. A review of all trials of NMDA or AMPA receptor antagonists and glutamate antagonists indicates no benefit from these agents in acute stroke. Metaanalysis of choline precursors in humans indicated a beneficial and substantial treatment effect, with an absolute reduction of 10–12% in long-term death and disability (OA 64, p553). A small randomized, double blind pilot trial of erythropoietin treatment in 20 patients began within 8 hours of symptom onset showed a better outcome on clinical and imaging parameters for the treated patients (OA 71, p354). However, expert commentary during the conference highlighted the idea that the results of neuroprotection studies in humans continue to be disappointing, compared with those achieved in animal models using the same agents. Reports of benefit using acute neuroprotective therapy in humans have been more closely associated with improvement in neuroimaging parameters than in clinical outcome. This discrepancy has included studies of citicholine and tirofiban (a GPIIb/IIIa-receptor antagonist).

Neuroimaging
Imaging of cerebrovasculature was discussed in abstracts and in a special symposium with magnetic resonance angiography (MRA), computed tomography angiography, and ultrasonography each proposed to be the superior test. Presenters each advocated for a particular modality, attendees were left with the impression that all are helpful in the appropriate context, and that the most effective modality at any institution will be the one performed by the most technologically proficient individuals. High field-strength MRI, utilizing up to 8 Tesla magnets (Tesla Engineering Ltd., West Sussex, England), is being studied in humans. This MRI technique was reported to be useful in assessing vascular plaque characteristics, although it was not compared with ultrasonography, which is generally effective and considerably less expensive.

The use of contrast-enhanced MRA was not significantly more helpful in examining the intracranial vasculature for aneurysms, according to one study from the Mayo Clinic (Rochester, MN) (P 12, p364). The authors noted that 3.0 Tesla images were of superior quality, but both 3.0 Tesla MRA and 1.5 Tesla MRA imaged 100% of 27 aneu-
rystms while 3.0 Tesla contrast-enhanced MRA found only 94.7% of the aneurysms.

**Emergency Treatment In Stroke**

Clinical use of acute stroke therapies in community hospitals continues to lag behind academic medical centers with stroke research programs. Stroke neurologists would like all physicians to be more aggressive in their approach to acute stroke treatment, especially those neurologists who do not take an active role in the treatment of acute stroke patients in emergency room settings (4). Two trials currently underway examine the utilization of emergency room physicians to manage acute stroke without direct help from neurologists. Presentations entitled, “Emergency Physicians Can Learn Acute Stroke CT Interpretation” (OA 42, p349) and “The Teleradiology Assessment of CT’s Online Reliability Study” (OA 43, p349) each provide support for a system allowing for the initiation of acute stroke therapy without neurologists. Since “time is brain” in acute stroke management, treatment in the field by EMS technicians would be ideal if agents with more optimal safety margins were available. The use of intravenous magnesium sulfate is being studied in the Field Administration of Stroke Treatment–Magnesium Sulfate (FAST-MAG) pilot trial (OA 66, p353). Diagnostic accuracy by paramedics in the field was excellent, and this pilot study demonstrates the feasibility of delivering neuroprotective therapy in the field. A larger, placebo-controlled trial is planned.

**Prothrombotic States and Stroke**

Transient monocular blindness (TMB) was found to be frequent in patients with systemic lupus erythematosus (SLE), with a calculated incidence of 422/100,000 compared with 14/100,000 in the normal population (P 173, p 393). One hundred seventy-five unselected patients were studied. At onset, 10 patients had experienced TMB. During a mean follow-up of 5.7 years, an additional four of 165 patients developed TMB. During this follow-up period, 10% of patients with TMB at baseline experienced a major vascular event compared with 5.5% of patients without TMB (OR 1.9, CI 0.2–16.9). The authors concluded that patients with SLE and TMB did not have a significantly increased risk of major vascular complications compared with those without TMB, but the statistical power may have been inadequate to say this with confidence.

Investigators in Perth, Australia examined inherited thrombophilias in ischemic stroke and their etiologic subtypes using 219 hospital cases of first-ever stroke versus case controls (OA #58, p352). Thrombophilia was present in 14.7% of stroke patients and 11.7% of controls. Thus, the association of thrombophilia with stroke may be coincidental. The investigators did not look at patients selected for age or for the presence of other factors suggesting a thrombophilia. This study confirms that physicians need to be selective in choosing tests for prothrombotic states in this clinical setting.

Kennemer et al. (OA 16, p 344) reported a multicenter, case-control study of ischemic stroke in 203 women using oral contraceptive pills (OCPs). Use of any OCP produces a stroke risk about 2.3 times greater than that among women who do not use these drugs. First-generation OCPs had a stroke odds ratio of 1.7 (95% CI 0.7–4.4), second-generation low-dose OCPs an odds ratio of 2.4 (97% CI 1.4–4.1), and third-generation OCP an odds ratio of 2.2 (95% CI 1.2–3.9), showing unexpectedly that the newer, low-dose OCPs are not safer in regard to stroke. As expected, other risk factors for stroke added to the total risk for stroke in women using OCPs.

**Neuro-ophthalmology**

Several papers that dealt directly with neuro-ophthalmic issues did not present substantially new information. In one study (P 67, p 374) of 280 patients referred to a stroke service, 23 had ocular bruits auscultated, only five of whom also had cervical carotid bruits. Surprisingly, the most frequent association was in patients with contralateral extracranial carotid stenosis or occlusion (65%), followed by patients with ipsilateral intracranial carotid stenosis (21%), and patients with a generalized hyperdynamic state (9%). Blood flow in the ophthalmic artery was examined in a study using Power-M Mode Doppler, insolated at 50–60 mm (P 47, p 370). Reversed ophthalmic artery flow was reported to be specific for >95% to 100% cervical carotid artery stenosis (P 47, p 370). No reversal of flow was seen in any patient with less than 95% stenosis of the ipsilateral cervical carotid artery. These results would have to be compared with prior studies of orbital blood flow for correlation. Central retinal artery (CRA) flow velocity was studied using Doppler flowmetry (P 53, p 371). Five measures of flow velocity were determined and then compared with the MRI-detected number of lacunes in the studied patients (P 53, p 371). There were correlations between numbers of lacunes in two of the five CRA velocity measurements. Interestingly, the number of lacunes was not correlated with the usual arteriosclerotic risk factors of hypertension, diabetes, age, hyperlipidemia, or smoking. Finally, low-contrast letter recognition using luminance-defined random dot letters was studied as a simple measure of postoperative cognitive function in patients after coronary artery bypass grafting (CABG) (P 73, p 375). The change in the luminance gradient needed for recognition of low contrast letters correlated with the number of microemboli detected during CABG.
REFERENCES


Neuroscience Journals

Reviewer: Synde Givre, MD, PhD

I. Apoptotic Neuronal Death After Ischemia

Formerly, necrosis was thought to be the process responsible for cell death after ischemia. In the past several years, many studies have provided evidence that ischemia results in apoptosis as well as necrosis, and that apoptosis may be responsible for delayed neuronal loss after ischemic injury.


The goal of the authors was to investigate the role of free radicals and the enzymes that normally detoxify them in apoptotic neuronal death induced by hypoxia. Neuronal cell cultures isolated from developing rat brain were exposed to 6 hours of a 78% decrease in the partial pressure of oxygen, then reoxygenated (experimental group), and were compared with identical cultures maintained at normoxia (control group). Intracellular levels of reactive oxygen species were significantly increased in the experimental cultures as compared with controls up to 48 hours after reoxygenation. Also in experimental cultures, the mRNA levels of Cu/Zn-superoxide dismutase and Mn-superoxide dismutase, both active in detoxifying free radicals, were transiently depressed during hypoxia, and then increased after reoxygenation. At 96 hours after reoxygenation in the experimental cultures, there was a 37% reduction in the number of living cells, and 23% of the living cells had nuclear apoptotic characteristics decreased to 4.6% but the percentage of necrotic cells was unaltered. NAC had no effect on intracellular free radical production that is detectable for several days after reoxygenation. Although there is a concomitant increase in the levels of mRNA encoding enzymes that detoxify free radicals, the anti-oxidant capacities of these enzymes may be overwhelmed, leading to apoptosis. NAC, a precursor of glutathione, appears neuroprotective.


The goal of the authors was to investigate the relationship between nitric oxide and apoptosis after ischemia. They compared the results of permanent, unilateral middle cerebral artery occlusion in normal mice to those of mutant mice lacking the gene for neuronal nitric oxide synthase (those with a deficiency in neuronal nitric oxide production). The mean infarct area was significantly reduced in mutant mice at 6, 24, and 72 hours after artery occlusion. The number of apoptotic neurons as assessed by terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL, a marker of DNA fragmentation) and by caspase-3 mediated cleavage of actin to fractin was significantly reduced (50%) in mutant mice as compared with wild type mice at 72 hours. This held true after normalization for the smaller infarct size in mutant mice. Also, the level of Bel-2, an anti-apoptotic protein, was significantly decreased (73%) in the ischemic hemisphere (versus the nonischemic, control hemisphere) of wild type mice and was significantly increased (105%) in the ischemic hemisphere (versus the contralateral hemisphere) in mutant mice. Levels of the pre-apoptotic protein Bax were unchanged in the ischemic hemispheres of mutant and wild type mice. The authors propose that deficiency in neuronal nitric oxide production slows the development of apoptotic cell death after ischemia.


Once terminally differentiated, neurons enter a resting state. Aberrant reentry into the cell cycle is believed to cause apoptosis. Such reentry may be induced by ischemia. The goal of the authors was to investigate the temporal relationship between the expression of various cell cycle
proteins and delayed neuronal death in mice after 30 minutes of reversible, unilateral occlusion of the middle cerebral and anterior choroidal arteries. Similar measurements were made in primary neuronal cultures after oxygen-glucose deprivation. Arterial occlusion led to cell death in the striatum but not the cortex. After 9 hours of reperfusion, before the appearance of any TUNEL staining, approximately half of the striatal neurons stopped expressing p16\textsuperscript{INK4a}, an inhibitor of cyclin-dependent kinase (cdk). Cdk is a cell cycle protein. These p16 negative neurons subsequently underwent cytoskeletal degradation and stained for TUNEL. TUNEL staining peaked at 72 hours after reperfusion and no TUNEL labeled cell expressed p16. In contrast, virtually all neurons surviving at 72 hours did express p16. Similarly, in cultured neurons, p16 and p27\textsuperscript{Kip1} (another inhibitor of cdk) were downregulated after oxygen–glucose deprivation. Furthermore, cyclin D1, an activator of cdk, was upregulated following cerebral ischemia and oxygen–glucose deprivation in vivo and in vitro, respectively. Such changes were not seen in control (sham operated) mice and in control cultures. When added to cultured neurons prior to oxygen–glucose deprivation, olomoucine, an inhibitor of cdk, significantly protected neurons from damage. These results provide evidence that cell cycle proteins are altered in postmitotic neurons after ischemic insult as a prelude to apoptosis. The authors hypothesize that these alterations represent attempts at cell cycle reentry.

II. Apoptosis in Multiple Sclerosis


Mechanisms of cell death resulting from inflammation in multiple sclerosis (MS) and the animal model of MS, experimental autoimmune encephalomyelitis (EAE), are not completely understood. The authors used electrophysiology and histology to investigate the function and morphology of retinal ganglion cells in rats after induction of EAE by intraperitoneal injection of recombinant rat myelin oligodendrocyte glycoprotein. Of the 17 immunized rats, seven developed widespread, bilateral demyelination of the optic nerves and swollen, distorted axons on histology. These seven rats had absent flash and pattern evoked potentials, markedly reduced pattern ERGs and normal flash ERGs as compared with control (sham injected) rats and experimental rats that did not develop demyelination on histology. Electrophysiological results were similar in control rats and experimental rats without demyelination. The density of retinal ganglion cells was evaluated by retrograde labeling using Fluorogold, a fluorescent dye that had been injected into both superior colliculi before induction of EAE or sham induction of controls. In rats with demyelination, the retinal ganglion cell density was significantly reduced at 50–72 hours after the onset of clinical symptoms (tail weakness). In EAE rats that did not develop demyelination, the retinal ganglion cell density varied greatly from normal (similar to control rats) to greatly reduced (as in EAE rats that did develop demyelination and symptoms). In rats with demyelination, some retinal ganglion cells stained positive for TUNEL and for caspase-3 activation.

In summary, EAE results in demyelination in rat optic nerve and a reduction in the number of retinal ganglion cells. The authors propose that the mechanism of retinal ganglion cell death is apoptosis and that their results give the molecular rationale for the early application of neuroprotective strategies in MS. However, given that markers for apoptosis were seen only in some remaining retinal ganglion cells, this proposal will require further investigation.

III. Neurotrophic Factors


Brain-derived neurotrophic factor (BDNF) is known to promote survival and differentiation of neuronal progenitor cells in culture and generate new neurons and glia in selected areas of adult mammalian forebrain in vivo. In the current study, the authors examined the distribution and types of newly generated cells in the adult rat forebrain 16 days after a 12-day continuous administration of BDNF (vehicle alone was administered in control rats) into the right lateral ventricle. To label the newly generated cells, the cell proliferation marker BrdU was administered intraventricularly, concurrent with BDNF (another control group consisted of rats receiving intraperitoneal injections of BrdU without any intraventricular infusion). Newly generated, BrdU\textsuperscript{+} cells were present in the subventricular zone surrounding the infused lateral ventricle as shown in previous studies. New cells were also found in areas not previously thought to give rise to them including the parenchyma adjacent to the lateral ventricle, the striatum, septum, corpus callosum, cerebral cortex, thalamus and hypothalamus. In some areas, new cells were found in the brain parenchyma and not in the adjacent subventricular zone. Nuclear diameter and morphology of labeled cells varied with location. Cells were frequently aggregated in pairs, possibly indicating that cell division had occurred. In control rats infused intraventricularly with vehicle plus BrdU, the number of newly generated cells was substantially less, though the distribution was similar to the distribution of new cells in the experimental group. In control rats receiving only intraperitoneal BrdU, the number of new cells was substantially

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less than in experimental animals and the distribution of new cells was restricted primarily to the subventricular zone adjacent to the lateral ventricle. In the experimental group, the distribution of BrdU labeling correlated well with labeling for TrkB, a high-affinity receptor for BDNF. However, TrkB labeling in infused hemispheres of experimental rats was not different from that in the uninfused hemispheres or from that in vehicle-infused controls. Thus, BDNF did not upregulate TrkB expression. Furthermore, TrkB+ cells were not themselves BrdU+ but were adjacent to BrdU+ cells. The percentage of BrdU-labeled cells that co-labeled for a neuronal cell marker varied from 27 to 42 and in all regions was significantly higher than the number of new neuronal cells in rats infused with vehicle. The authors conclude that BDNF profoundly increases the cell proliferation and survival of progenitor cells and their progeny. The fact that areas of higher new cell density were not necessarily closer to the subventricular zone may indicate that progenitor cells are normally present in situ. Variations in new cell density could be the result of variations in TrkB expression. Future studies will investigate whether BDNF can rescue degenerated neurons or replace neurons already lost as a result of disease.


In recent years, therapeutic strategies for neurodegenerative diseases have been proposed that address cell loss rather than replacement of neurotransmitters. These strategies have included replacement of dead neurons with new ones via transplantation and prevention of neuronal death using trophic factors. Glial cell line-derived neurotrophic factor (GDNF) is known to be a potent neurotrophic factor for substantia nigra dopaminergic neurons. The authors of the current study sought to determine if the delivery of GDNF by transplanted neural stem cells could exert a therapeutic effect in a mouse model of Parkinson’s disease. A stable clone of mouse neuronal stem cells expressing neural stem cells integrated and differentiated well after grafting, dispersed within but remained restricted to the striatum, and maintained GDNF expression for at least 4 months. Furthermore, grafting afforded protection of dopaminergic neurons. To determine if GDNF grafting conferred functional protection in the lesioned mice, two motor behavioral assays were performed 12 and 13 days after lesioning. Lesioned mice that had received GDNF grafts performed significantly better than lesioned mice that had received the mock graft or lesioned mice that had not received any graft.

The delivery of genes by neural stem cells has the advantages that no genetic modification is introduced in the host cells and no viral particles are introduced into the nervous system. In grafting over 100 mice in these experiments, none developed a tumor. The results of the current study suggest that transplantation of genetically engineered neural stem cells could be an effective strategy to locally deliver trophic factors to the brain because GDNF-expressing neural stem cells integrated and differentiated well after grafting, dispersed within but remained restricted to the striatum, and maintained GDNF expression for at least 4 months. Furthermore, grafting afforded protection of dopaminergic neuron survival and prevention against motor disturbances in a mouse model of Parkinson’s disease. Graft survival was greatly enhanced in nude mice, suggesting that some form of immunologic modulation may be necessary when applying this technique to immunologically normal subjects.


Insulin-like growth factor-I (IGF-I) is a potent neurotrophic factor that is present in brain. The goal of the authors was to determine the effects of IGF-I on long-term neuronal outcome and somatosensory function after right carotid artery ligation followed by short inhalational
that received FGF2 or NGF had a dramatic increase in the number of fibers regenerating into the dorsal horn as compared with animals receiving control injections. In addition, rats receiving injections of NGF had a dramatic increase in the amount of sprouting of spared axons from L3 and L6. Regenerated sensory afferents were observed in normal and abnormal laminae and both within gray and white matter of the dorsal spinal cord. Axonal growth was greatest within the regions surrounding the injection sites. Injection of L1 did not induce axonal growth. Nociception and proprioception were tested in a double-blind fashion. After rhizotomy but before adenoaviral vector injection, rats had a complete loss of thermal sensation ipsilaterally but not contralaterally. After injection of either control marker or L1 in to the dorsal horn, rats showed no recovery of nociception or proprioception. Rats injected with either FGF2 or NGF gradually recovered nociceptive function. This was first apparent at one week after injection and reached statistical significance, achieving near-normal values by week 2 to 3. There was a correlation between the recovery of nociceptive function and the regeneration of axons on histology. Furthermore, cutting L4 and L5 after recovery abolished ipsilateral nociception, indicating that it was not due to collateral sprouting from L3 and L6. Proprioceptive functioning was not improved after injection of control marker, NGF, FGF2 or L1. The authors thus demonstrated that in vivo expression of NGF and FGF2 can induce axonal regeneration and functional recovery of nociception, supporting the use of in vivo gene therapy as a means of delivering molecules able to transform the adult CNS from inhibitory to growth-promoting.

IN OTHER JOURNALS


Lens epithelium-derived growth factor (LEDGF) is a transcription activator present in the nucleus of many cells types including the RPE and retinal photoreceptors. Previously, LEDGF had been shown to rescue damaged photoreceptors in chick and mouse models. The current study used a mouse retinal explant model to assess the rescue ability of LEDGF. At postnatal days 2 and 7 (PN2 and PN7, respectively), retinal explants were obtained from rd/rd mice, an animal model for the human recessive form of retinitis pigmentosa, and were compared with explants from wild type mice obtained on the same postnatal days. Wild type and rd/rd explants were incubated both with and without LEDGF. Untreated PN2 and PN7 explants from rd/rd mice had excessive loss of photoreceptors. LEDGF had no significant effect on wild type explants obtained from PN2 and PN7. LEDGF treatment significantly rescued the photoreceptors in both the PN2 and PN7-derived rd/rd explants.
Numerous kind. They fired bursts of activity after saccades previously been found in VI. Mixed cells were the most moved the AR by only a fraction of its width. Direction.

These cells were activated even by small saccades that perceived retinal motion was in the cell's preferred direction. These cells were activated even by small saccades that direction. These cells were activated even by small saccades that direction. These cells were activated even by small saccades that direction. These cells were activated even by small saccades that direction.

IV. Electrophysiology


When the head is immobilized and a subject attempts to maintain fixation on an object, fixational eye movements maintain visibility of the object. These fixational eye movements consist of slow drifts interspersed with small, fixational saccades. Whether the slow drifts alone or the combination of slow drifts and fixational saccades is necessary to maintain visibility is not known. The goal of the authors was to investigate the effects of fixational eye movements on single neuron activity in area V1 of macaque cortex. Subjects viewed a stationary stimulus on which they were trained to fixate. In addition to the temporal relationship between neuronal activity and fixational eye movements, the spatial relationship between the receptive-field activating region (AR) and the stimulus that was established by the eye movement was investigated. Recordings revealed three types of neurons, position/drift-activated cells, saccade-activated cells and mixed cells. Position/drift-activated neurons were activated during the intersaccadic drift period when an optimal stimulus was within the cell’s AR. This type of cell exhibited an increase or decrease in firing after a saccade, depending on whether the saccade moved the AR onto (or better centered over) or off of (or more poorly centered over) the stimulus, respectively. The activity of saccade-activated cells was complimentary to that of position/drift-activated neurons. Saccade-activated neurons discharged when a fixational saccade moved the AR onto, off of or across the stimulus. Some saccade-activated cells were direction sensitive and were activated when the AR moved both off and onto the stimulus as long as the perceived retinal motion was in the cell’s preferred direction. These cells were activated even by small saccades that moved the AR by only a fraction of its width. Direction selectivity for activation by a fixational saccade had not previously been found in V1. Mixed cells were the most numerous kind. They fired bursts of activity after saccades and exhibited more irregular, sustained activity during the intersaccadic drift periods.

The authors hypothesize that, during natural viewing conditions, position/drift-neurons may be important in signaling the position of stimulus features on the retina and may be refractory to the detrimental effects of saccades. The response of saccade-activated neurons, being ambiguous with respect to the spatial details of the retinal image, may be involved in constructing a stable world in spite of constant retinal image motion. Alternatively, saccade-activated neurons may be involved in the suppression of visual input associated with saccades.


The a-wave of the dark-adapted ERG is classically thought to represent the activity of rod photoreceptors but several studies have shown that the inner retina may also contribute to this potential. The goal of the authors was to use pharmacologic agents to determine if, in primates, the Ganzfeld ERG dark-adapted bright flash a-wave primarily reflects the activity of photoreceptors or whether it contains a component of inner retinal activity. ERGs were recorded from anesthetized macaque monkeys before and after intravitreal injections of 4-phosphono-butyric acid (APB), which blocks depolarizing-bipolar cell activity and cis-2,3-piperidine-dicarboxylic acid (PDA), which blocks hyperpolarizing-bipolar cell, horizontal cell and amacrine cell activity. Light-adapted cone responses were subtracted from dark-adapted ERGs elicited over a 5-log-unit intensity range to isolate the rod ERG a-wave. The results showed that for bright, short flashes, the application of APB or PDA had no effect on the leading edge of the a-wave up to the point of intrusion of the b-wave. Therefore, the a-wave elicited by a bright, short flash is dominated by the activity of rod photoreceptors. APB reduced the dark-adapted maximum a-wave amplitude and PDA increased the dark-adapted a-wave maximum amplitude. Neither chemical changed the shape of the waveform. This suggests that APB and PDA can alter the maximum dark current flowing from the rod inner to outer segment. Since APB and PDA are not known to have any effect on photoreceptors themselves, this alteration of current may reflect feedback from postreceptor cells.


The anatomic substrate for long-range interactions amongst single neurons in primary visual cortex exists in
the extensive dendritic and axonal arborizations of pyramidal cells. The physiologic and functional implications of these lateral connections are still not well understood. The goal of the authors was to study the nature of the modulation of the responses to stimuli in the classic receptive field (CRF) by simultaneously presented remote stimuli. Single unit recordings were obtained from primary visual cortex of adult cats. Stimuli were composed of three distinct patches (Gabor patches). The center patch (target) matched the retinotopic location, orientation, size and spatial and temporal frequency selectivity of the classic receptive field of the neuron being recorded from. Two flanker patches were presented well outside the classic receptive field. In any given cell, the response to the target could either be facilitated or suppressed by the flankers when the orientation of the flankers matched that of the target. Rather than depending on the absolute contrast of the flankers, the sign of the modulation (facilitation versus suppression) seemed to be determined by the contrast of the flankers relative to the threshold contrast of the target. At contrasts just above the neuron’s firing threshold, facilitation most often occurred. At higher contrasts suppression most often occurred. Such modulation was obtained at 12 degrees or more of separation of the target and flankers. If the orientation of the flankers was made orthogonal to that of the target, facilitation was lost. These results were found in simple and complex cells and in cells in the supragranular, granular and infragranular layers of cortex. The authors hypothesize that the effects of remote stimulation provide the basis for a neural mechanism for the perceptual grouping of stimulus features belonging to a large, complex scene.


Chloride channels are proteins known to be important in salt and fluid movement and cell volume regulation. Based on their previous work, the authors hypothesized that changes in cell shape and/or volume are necessary for migration of human glioma cells and that Cl\textsuperscript{−} currents may effect such changes. The current study used patch-clamp techniques to investigate Cl\textsuperscript{−} currents, in particular volume-activated Cl\textsuperscript{−} currents, in two human glioma cell lines. Also, an in vitro model of invasive migration was used to investigate the role of Cl\textsuperscript{−} currents in invasion. Exposure of the cells to hypotonic solutions led to swelling of the cells and activation of currents with electrical properties characteristic of Cl\textsuperscript{−} currents. Such currents were >80% inhibited by the application of several well known antagonists of the volume-activated Cl\textsuperscript{−} channel including tamoxifen and 5-nitro-2-(3-phenylpropylamino)-benzoate (NPPB). Furthermore, when the relative permeabilities of I\textsuperscript{−} and Cl\textsuperscript{−} were compared, these currents had ion specificities similar to those of known volume-dependent Cl\textsuperscript{−} channels. To look for resting Cl\textsuperscript{−} currents, Cl\textsuperscript{−} was replaced by poorly permeant ions. This led to a reduction of outward current and a positive shift in the reversal potential of the cells, providing evidence for a resting Cl\textsuperscript{−} conductance. In the in vitro model of invasive migration, cells were plated on a plate with a filter consisting of pores that provide a three-dimensional constraint to movement. The pores were of such a size that cells were required to change their shape to navigate through them. Placement of a chemoattractant agent on the side of the pores opposite the cells led to migration of the cells through the pores. This migration was reduced in a dose-dependent fashion after the application of NPPB. Spontaneous movement of glioma cells during patch-clamp recording was also observed using time-lapse video recording. This spontaneous movement was accompanied by an increase in the whole-cell current in a manner consistent with Cl\textsuperscript{−} currents. Application of NPPB stopped the movement.

The authors propose that volume-activated Cl\textsuperscript{−} currents are important in generating the cell size and volume changes necessary for the migration of glioma cells through the extracellular spaces in brain.


The vestibulo-ocular reflexes (VOR) are critical in maintaining stable image perception during motion. Previous studies have shown that, with regards to the rotational VOR (RVOR), a disynaptic connection exists between the vestibular sensory organ and the ocular motor nuclei, while the initial synapse being in the rostral vestibular nuclei. The shortest latency RVOR pathways are mediated predominantly by excitatory projections to the contralateral sixth nerve nucleus. The pathways for the translational VOR (TrVOR) are less well understood. The goal of the authors was to investigate the activity of single neurons in the rostral vestibular nuclei of rhesus monkeys during pursuit eye movements, RVOR, TrVOR (with the subject fixating on an earth-fixed target) and suppression of the RVOR and TrVOR (with the subject fixating on a head-fixed target). Based on their preferred stimulus patterns, neurons were classified into two broad categories, eye-contra and eye-ipsi cells that responded to contralateral and ipsilateral eye movements, respectively. Further subtypes of neurons
were then defined. Burst-tonic (BT) neurons were sensitive to eye movements, behaving similarly during rotation and translation, but were inactive during VOR suppression. Vestibular-only neurons were insensitive to smooth pursuit eye movements in the absence of rotational or translational head movement. Position-vestibular pause (PVP) and position-vestibular (PV) cells were sensitive to rotational head movement and eye movement in opposite directions (with these movements performed either in isolation from each other or together). Eye-contralateral PVP and PV neurons exhibited no response to ipsilateral head translation when it was isolated from eye movement activity in the TrVOR suppression task whereas eye-ipsilateral PVP and PV neurons did respond to translational head movement without eye movement. Eye-head (E-H) neurons were sensitive to rotational head movement and eye movement in the same direction (with these movements performed either in isolation from each other or together). In contrast to the eye-contralateral PVP and PV cells that exhibited no response to TrVOR, 50% of E-H neurons exhibited activity when the animal suppressed its eye movements.

In summary, most eye movement sensitive neurons exhibited activity during RVOR, RVOR suppression and TrVOR but only a subset, eye-ipsilateral PVP and PV neurons plus some of the E-H neurons, were activated during TrVOR suppression. This subset of neurons may be the recipient of more direct otolith signals and the authors suggest these neurons may form the cellular basis of the utriculoabducens pathway. A model of this pathway is constructed by the authors and discussed.

V. Anatomy


The exact molecular mechanisms underlying the development of topographic connections in the visual system of chicks and mammals are controversial and not completely understood. Spatial concentration gradients of certain topographic guidance molecules play an important role. In chicks, EphA receptors and their ephrin-A ligands act as such guidance molecules in the development of connections between retinal ganglion cells (RGC) and the tectum. The goal of the authors was to determine the mechanisms that chick RGC use to develop their topographic projections to the tectum. First, topographic specificity in growth cone targeting, axon branching and arborization were quantified in vivo. RGC axons were labeled by injection of dye into defined retinal locations on embryonic day 9 (E9), when axons are initiating branching in the tectum, through E12, when definitive topographic organization can be identified. The retina and contralateral tectum of each subject were whole mounted and evaluated microscopically 12–72 hours later.

For each embryonic day, the termination zones (TZ) of axons and their arbors in the tectum were compared with the predicted TZ based on the distance of the injection from the temporal edge of the retina. For subjects injected at E13, by which time topography is correctly established, the observed TZ was always found to be at the predicted TZ, confirming the accuracy of the method of prediction of the TZ.) Normally, RGC axons develop their topographic map along the anterior–posterior (A-P) axis of the tectum with the temporal peripheral retina projecting to the anterior pole of the tectum. The labeling patterns revealed that retinal ganglion cell axons overshot the topographic location of their predicted TZ along the A-P tectal axis by a distance that varied with their origin along the temporal–nasal retinal axis (temporal axons overshot by the greatest amount). In contrast, branches formed along the axons with a topographic bias for the correct A-P location of the predicted TZ. Both branch distribution and density increased in topographic specificity between E10 and E13. Even at E10, though, the topographic bias in branch distribution for the predicted TZ was statistically significant. Refinement of topographic specificity was achieved by both axonal branch addition and branch elimination. Next, an in vitro assay was set up in which explants of temporal or nasal retina from E6 chicks were placed on a substrate of alternating lanes of membranes prepared from anterior or posterior tectum from E9–E10 chicks. Using this assay, temporal retinal axons were shown to preferentially target anterior tectal membranes. Ephrin-As are normally present in a higher concentration in the posterior tectum and preferentially repel or collapse temporal RGC axon growth cones. After the addition of EphA3-Fc to the assay, which blocks ephrin-A function, temporal axons branched equally on anterior and posterior tectal membranes. Finally, time-lapse video microscopy was used to investigate axonal branching in vitro. Both de novo branching from the axon shaft and bifurcation of the growth cone occurred. Axons from temporal retina exhibited preferential extension of branches onto anterior membranes although a bias to retract branches from posterior membranes acted to sharpen the topographic specificity of branch distribution.

These findings show that, rather than topographic growth cone targeting, topographic branching along the shaft of RGC axons is the critical event in the development of the retinotectal map in chicks.
Neuroclinical Journals

Reviewer: Kathleen B. Digre, MD

I. Wegener’s Granulomatosis


The authors prospectively analyzed 128 patients with documented Wegener’s granulomatosis diagnosed by American College of Rheumatology classification criteria. Internists, ophthalmologists, otorhinolaryngologists, and neurologists examined all patients. All had serologic assessment, chest computed tomography (CT), and cranial magnetic resonance imaging (MRI). Sixty-four patients (50%) had central (9 patients) or peripheral (56 patients) nervous system involvement. In keeping with practical experience, but contrary to previous reports, cranial nerve involvement was rare, occurring in only 6 patients (optic nerve 4, trigeminal and facial nerves 1 each). All cranial neuropathies were caused by infiltration originating in the paranasal sinuses. A distal symmetric peripheral neuropathy was the most common nervous system involvement. Patients with neurologic involvement were more frequently male, older at the onset, had a larger disease extent, and higher antineutrophil cytoplasmic antibody titers than those without neurologic involvement. Treatment with immunosuppression had a moderate effect.

II. Anticonvulsant Toxicity


The anticonvulsant vigabatrin is reported to constrict the visual field in 40% of treated adults and 65% of treated children. The drug increases the concentrations of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). The mechanism of visual field constriction is not clear. Tiagabine, another new anticonvulsant, has also been reported to cause visual field defects. It may also increase GABA by inhibiting GABA reuptake. In this study, the authors measured GABA concentrations in the brain and retina in adult male rats after administration of vigabatrin or tiagabine. Vigabatrin accumulated in the retina and caused accumulation of GABA in the retina at 5-fold the amount in the brain. Tiagabine did not accumulate in the retina or affect GABA concentrations there. The authors concluded that vigabatrin accumulation and perhaps an increase in GABA concentration may be responsible for the visual field constriction. Tiagabine was considered unlikely to cause visual field defects in humans.


The authors performed Goldmann perimetry on 60 adults who had been treated with vigabatrin for 7 months to 14 years as either single therapy or add-on therapy in partial epilepsy. Bilateral concentric visual field constriction was present in 40% and severe constriction in 13%. Follow-up visual fields after 4 to 38 months (mean of over 12 months in 55 patients) showed no change.


This is a postmortem case of a man who had taken vigabatrin 6 g/d for 5 months, then 5 g/d for 12 months, and finally 3 g/d for 7 months. Four months before his death, he developed trouble seeing houses along the street. He had bilateral concentric constriction of the visual fields with normal optic discs. On pathologic examination, the peripheral retina showed severe loss of ganglion cells and partial loss of nuclei from the inner nuclear layers. Mucosal fibers were preserved. There was no edema of the axon or myelin. The authors propose that the ganglion cell loss and damage to certain parts of the retina accounts for the variability of optic nerve atrophic changes seen and also the abnormality of the b-wave in the electroretinogram (ERG) findings.

These three studies strongly suggest that vigabatrin causes visual field constriction. The loss may be permanent in some cases. Ganglion cells appear to be damaged. Although tiagabine also affects GABA, there is no experimental animal evidence that it accumulates in the retina.

III. Infectious Disease


The authors analyzed the pattern of visual loss to the optic nerve, chiasm, and retrochiasmatic area in cysticercosis diagnosed by pathologic imaging, and/or cerebrospinal fluid (CSF) examinations. Visual loss, defined as loss of acuity of 20/40 or worse, occurred in 23 (8%) of
284 patients. Optic nerve damage (13) occurred most commonly from papilledema. Nearly all patients (12) had hydrocephalus. In four patients, chiasmal damage was caused by subarachnoid cyst or inflammation. Six patients showed retrochiasmal lesions due to parenchymal or subarachnoid cysts, or infarction of the visual radiations. The author recommended aggressive treatment of disc swelling by optic nerve sheath fenestration or correction of underlying hydrocephalus with shunting.

V. Increased Intracranial Pressure


The authors prospectively evaluated 114 patients with at least a 6-month history of chronic daily headache and 28 control subjects with other neurologic or psychiatric conditions. All patients underwent MRI and MRV; no patient had other confirming studies. Any patient with increased pressure of greater than 200 mm water had an ophthalmologic examination to exclude papilledema. The authors divided patients by MRV findings: group 1 (103) had normal MRV; group 2 (6) had irregular flow in the distal transverse sinus; group 3 (5) had irregular and absent flow in both sinuses. Then 30 patients were randomly selected from group 1 to undergo LP, as were all patients in groups 2 and 3. Not unexpectedly, group 1 and controls had normal lumbar puncture opening pressures (<200 mm CSF), whereas patients in group 3, four of five patients had elevated intracranial pressure. The patients in groups 2 and 3 were presumed to have had cerebral venous thrombosis (CVT). The headache characteristics in the 3 groups were indistinguishable; the CVT groups (2 and 3) were overweight compared with group 1 or controls. The authors concluded that CVT mimics idiopathic intracranial hypertension and that CVT should be looked for in all patients with chronic daily headache.

The biggest problem with this study is that the authors assume that because there are MRV irregularities, the veins are occluded. In fact, one of the examples of irregularity of venous structure that they cite is an arachnoid granulation—a normal variant. Furthermore, in a recent study (King JO, Mitchell PJ, Thomson KR, et al. *Neurology* 2002; 58:26-30), increased intracranial pressure itself led to elevated venous pressures and apparent stenosis within the transverse venous sinuses that reversed itself when the pressure was lowered. While we certainly want to exclude increased intracranial pressure in patients with chronic daily headache, accurate diagnosis of venous sinus obstruction still eludes us.


Unilateral papilledema from increased intracranial pressure is rare. These authors found only 15 cases from a combined 24-year experience, and could only find 11 reported cases in the literature. All patients reported were studied with detailed ophthalmoscopy and indirect ophthalmoscopy, as well as perimetry. Ten of the 15 cases with unilateral papilledema had idiopathic intracranial hypertension (IIH). The authors suggested that the symptoms and signs in patients with unilateral papilledema do not differ those in patients with bilateral papilledema. The authors propose that, in spite of its rarity, unilateral optic disc edema be considered as a manifestation of papilledema, and that an appropriate work-up be conducted.

V. Myasthenia Gravis


Acetylcholine receptor antibodies are present in the serum of almost 85% of patients with myasthenia gravis (MG). Anti-striated muscle antibodies have been a marker for thymoma, but are not specific for MG or thymoma. Antibodies to other antigens, including titin, one of the largest molecules in striated muscle, are being evaluated as markers for underlying thymoma. The authors studied a group of 398 patients with generalized MG (243 who had undergone thymectomy and 155 who had not) and 247 control patients (including normal subjects and patients with other autoimmune or neurologic conditions). Titin antibodies were found in 80% (56/70) of MG patients with thymoma, but in only 11% (17/165) of MG patients without thymoma. When titin antibodies were present in patients older than age 60 without thymoma, they were a marker for MG. In patients less than 60 years of age, the presence of titin antibodies increased the likelihood of thymoma.

See also the editorial that accompanies this article, Aarli JA. Titin, thymoma and Myasthenia Gravis. *Arch Neurol* 2001,58:869–70.


In contrast to the above study, these authors studied titin and two cytokines, interferon α (IFNα) and interleukin 12 (IL12), in 191 patients with myasthenia gravis (MG)
who did and did not have thymoma, and compared them to 82 controls. Titin antibodies were uncommon in patients younger than 40 years of age. Although they were more common in older patients, titin antibodies did not distinguish between those with or without tumor. Titin antibodies were not present in controls, or sero-negative MG. Cytokine antibodies were more common in individuals with thymoma. Furthermore, these antibodies increased if thymoma recurred. The authors concluded that titin antibodies are of limited importance in predicting thymoma (except in those younger than 60 years of age), but IFNα and IL12 may be important to predict recurrence in patients with MG who have thymoma.

From the above studies, it appears that in a patient with MG who is younger than 60 years of age who has equivocal thoracic imaging, titin antibody may be suggestive of thymoma. IL-12 and IFNα may be sensitive to recurrence of thymoma.

VI. Multiple Sclerosis


In a postmortem study, the eight brains of patients who died of multiple sclerosis (MS) disclosed smaller optic nerves and optic tracts and reduced axonal densities compared with normal brains. Although the size of the magnocellular cells of the lateral geniculate nuclei was equal, the parvocellular cells were significantly smaller and contained atrophic neurons. The authors believe that their findings support the hypothesis that the smaller axons in MS patients are more susceptible to injury than are the larger axons. This fact might help to explain in part why color vision (a parvocellular function) is preferentially affected over motion (a magnocellular function) in MS.


This is a review by an international panel that convened in London in 2000 from several countries to review criteria for diagnosis of MS and incorporate modern imaging criteria. The clinical guideline of finding objective lesions in space and time is still essential. Clinical evidence cannot be based on history alone; there must also be objective evidence. Imaging criteria for a diagnosis of MS include 3 of 4 of the following: 1) one gadolinium enhancing lesion or 9 T2 hyperintense lesions; 2) at least one infratentorial lesion; 3) at least one juxtacortical lesion; 4) at least 3 periventricular lesions. Cerebrospinal fluid (CSF) evaluation is also of value for the presence of oligoclonal IgG bands. CSF should show less than 50 lymphocytes. VEP is helpful as an adjunctive test to supplement information or to look for objective evidence of a second lesion. The panel rejected the terms “definite MS,” “probable MS” and substituted “MS,” “possible MS” (those at risk, but the diagnostic evaluation is not definite), or “not MS”.

VII. Vertigo


Visual vertigo, a frequent complaint, is characterized by symptoms provoked by visual contexts such as supermarkets, driving, or moving objects. In this study, 17 of 21 patients diagnosed with visual vertigo by history (vertigo worsened by visual surroundings like crowds, grocery store aisles) were diagnosed as having a peripheral vestibular disorder (history of vestibular neuritis, benign positional vertigo, basilar migraine). The 21 patients with visual vertigo were compared with 25 normal controls without history of neurologic or vestibular disease and 16 patients whose testing documented bilateral labyrinthine defect subjects (LDS). Questionnaires showed that trait anxiety scores (from the Spielberger Trait Anxiety Inventory) and childhood motion sickness were similar in all the three groups. However, vertigo symptom scales of autonomic symptoms were higher in both of the patient groups compared with controls.

Furthermore, patients with visual vertigo had similar vertigo handicaps as those with bilateral labyrinthine defects. The three groups were next tested by psychophysical experimental stimuli including testing the subject’s sense of vertical in darkness and on variously tilted frames and by measuring postural sway (a standing platform that measured an individual’s head and body movement) under different conditions (eyes closed, eyes open, viewing a visual target on a tilted frame and on a rotating disc). Patients with visual vertigo and LDS both showed larger tilts of the visual vertical than normal controls. This indicates that those with visual vertigo as well as those with LDS are dependent on visual clues for perception. The postural sway patterns were expressed in quotients: The Romberg quotient was the sway path generated with eyes closed divided by the sway path generated with eyes open. Patients with visual vertigo behaved like normal controls in that the sway path was almost equal in both conditions, whereas the patients with LDS had an increase in this quotient. However, another quotient, the visual-kinetic quotient, which showed the sway path during the disc rotation divided by the sway path with the eyes open showed that patients with LDS...
behaved more like normal controls whereas the disc rotation in patients with visual vertigo caused a much larger sway path. Visual vertigo patients therefore have larger perceptual and therefore postural responses to disorienting visual stimuli, and visual vertigo occurs when individuals have an over dependence on visual inputs. The authors suggest that patients with visual vertigo could be treated by visual motion desensitization.

Visual vertigo is a common symptom presenting in neuro-ophthalmic and neuro-otologic clinics. This study begins to tease away at the complexity of the symptom. Further, it suggests that just as benign positional vertigo is treated with habituating exercises, visual vertigo may respond to motion desensitization exercises.

VIII. Migraine


The authors looked for non-heme iron deposition in the periaqueductal gray matter on 3.0 Tesla MRI in 17 patients with episodic migraine (EM), 17 patients with chronic daily headache (CDH), and control subjects. They found that there was a significant increase in iron in both of the EM and CDH patients as compared with control subjects. There was no difference between the CDH and EM patients and no difference between migraine patients with or without aura. The authors concluded that iron homeostasis in the periaqueductal gray area is progressively impaired by repeated attacks of migraine. They propose that the periaqueductal gray area is the "generator" of migraine attacks by loss of inhibitory control of nociceptive spinal afferents. Iron deposition, perhaps a marker of oxidative stress and free radical damage, may be the "burden of illness."

This study is important because it not only corroborates earlier PET studies that showed increased regional blood flow to the midbrain structures (periaqueductal gray, midbrain reticular formation and locus ceruleus) as a "generator" of migraine, but also because of the implications for the pathophysiology and long-term sequela of migraine.


The authors reviewed compared 130 patients with active migraine at the time of stroke to those with stroke without migraine from the Lausanne Stroke Registry. Among migraine patients, half were younger than 45 years of age; most were women (74%, younger; 63% older than 45). The prevalence of migraine in the younger stroke group was 23% in women and 8% in men. This rate reflects what is known about prevalence of migraine in the general population of this age group. The younger patients had less anterior circulation strokes and a patent foramen ovale, while the older patients had none of the usual vascular risk factors (hypertension, ischemic heart disease or smoking). Compared with patients who had ischemic stroke without migraine, women with migraine were more frequently on oral contraceptives (controls 30%, migraineurs 45%). Interestingly, in the younger group, arterial dissection was less frequent in patients with migraine than in controls. Only 9 patients developed stroke during a typical aura and 15 developed stroke during migraine without aura. These authors also found that a patent foramen ovale was four times more common in migraine-stroke patients. These authors reiterated that in older individuals, active migraine is infrequent as a cause of stroke. They suggested that in younger migraine-stroke patients, patent foramen ovale should be investigated, but do not provide any basis for concluding that this anatomic variant was associated with paradoxical embolism.

IX. Visual Fields


The preserved temporal crescent on visual field examination is touted as a specific sign for contralateral occipital lobe pathology. The author reviewed 16 patients with a partial or complete monocular preserved temporal crescent as assessed by Goldmann perimetry. Imaging was performed in 15 patients. Lesions were due to stroke, birth injury, trauma, aneurysm and migraine. Most lesions were medial occipital lobe infarcts, but 19% (3/16) had lesions of the optic radiations. Spontaneous visual hallucinations were present in 44% of patients. The author asserts that the preserved temporal crescent is less likely to be diagnosed now that automated static perimetry—which usually samples only the central 30 degrees of field—has replaced kinetic Goldmann perimetry.

X. Genetic Disorders


See also the editorial,
Chronic progressive external ophthalmoplegia (CPEO) is usually caused by large deletions in mitochondrial DNA, but point mutations have also been described. Several new genes have been linked to this disorder. One new gene, adenine nucleotide translocater 1 (ANT1), has recently been associated with the autosomal dominant form of PEO (adPEO). Found in 11% of patients with adPEO, it is responsible for transporting ATP across the inner mitochondrial membrane. Twinkle, another name for a gene associated with adPEO, is found in 15% of patients with adPEO and may be involved in mitochondrial replications. A third mutation, polymerase gamma (POLG), is also responsible for mitochondrial DNA replication. How ANT1, Twinkle, or POLG cause PEO is unclear. The first of these three papers describes two further point mutations, including a single nucleotide in the tRNA in a single individual who exhibited CPEO, myopathy, exercise intolerance, and elevated serum lactate. The second report is of a mutation in L98PANT1 in a Greek family who had mild ptosis and PEO; one individual had pigmentary retinopathy. The accompanying editorial tries to synthesize what is known in PEO genetics.

XI. Apraxia of Eyelid Opening


Apraxia of eyelid opening (ALO) is the inability to open the eyes voluntarily in the presence of intact spontaneous eye opening. While apraxia occurs most often in conjunction with blepharospasm, it can occur with other conditions such as progressive supranuclear palsy (PSP) and Parkinson’s disease. The authors studied 12 ALO patients (11 with blepharospasm) and 12 controls, using EMG of the orbicularis oculi and lid movement recordings. Not unexpectedly, lid opening latencies and lid movement duration were increased in ALO patients compared with controls. Persistent orbicularis oculi activity was detected by EMG in 11 ALO patients and thought to be the explanation for the delay in lid opening in these patients. This study suggests that ALO is a subclinical form of blepharospasm.

XII. Pituitary Disease


The authors reviewed 30 patients with acute pituitary apoplexy who had undergone thorough neurologic and neuro-ophthalmologic examinations. Patients were divided into groups based on the presence or absence of precipitating factors. Only 6 of the 30 patients had a previously diagnosed pituitary adenoma. Conditions associated with apoplexy were found in 9 (30%) patients, including recent anticoagulation (3), thrombolytic therapy (1), an antecedent surgical procedure (2), the postpartum state (1), treatment of cellulitis (1), and discontinuation of bromocriptine therapy (1). In addition to treatment of the underlying endocrine dysfunction, 27 patients underwent surgical decompression. The group with identifiable associations had more altered consciousness preoperatively than those who had no such associations.

This study demonstrates two important points. First, most pituitary apoplexy does not occur in previously diagnosed adenomas. Second, pituitary apoplexy has few associated conditions, which makes this diagnosis unpredictable.

XIII. Degenerative Conditions


The authors studied the MRI characteristics of the brain stem in patients with Parkinson’s disease (20), progressive supranuclear palsy (PSP) (16), and multiple system atrophy (MSA) (14). The antero-posterior diameter of the midbrain was found to be the best separator. Parkinson’s patients and controls were similar, while those with PSP had significantly lower diameters. Interestingly, the midbrain diameter in MSA was also lower than in controls and in Parkinson’s disease, but not as low as in those with PSP.
The Neurology of Vision


Scope: This is a carefully compounded and well referenced text that describes in detail the anatomy, physiology, and function of the optical, retinocortical, and integrative components of the human visual system. The book is Volume 60 in the Contemporary Neurology series, which is intended for neurologists, but the material is equally relevant for ophthalmologists. In fact, some sections are more ophthalmologically than neurologically oriented and provide a quick eye reference for neurology types.

The author is a rare bird, board-certified in both neurology and ophthalmology, and uniquely qualified to add a thorough review of disorders of visual perception for the renowned Contemporary Neurology series. Dr. Trobe is a coauthor of the largely algorithmic Clinical Decisions in Neuro-Ophthalmology, but he has now turned to the more familiar topical discussion formula; his discussions are very complete, indeed.

Contents: The section on the afferent system alone runs to more than 400 pages and encompasses six areas that include: “How the Human Visual System Works,” “Symptoms of a Failing Visual System,” “Measures of a Failing Visual System,” “Topographic Disorders,” “Nonorganic Visual Disturbances,” and a final section of “Problem Cases: Questions and Answers.” There are 18 Chapters, ranging in topics from a primer on optics, discolored images, provoked transient visual deficits, failed recognition, visual field interpretation, electrophysiologic evaluation of visual loss, retinal and choroidal vascular disease, and toxic retinopathies. Especially noteworthy is the material related to posterior visual pathways and cortical and visual integrative functions. The diagrammatic illustrations of Tanya Leonello will be an aid for all. The abundant use of tables, carefully considered clinical illustrations, and reproductions of neuroimages are highlights that add further value to this new text.

The section on “Problem Cases: Questions and Answers” is an innovative and highly instructional exercise. It is difficult to write multiple-choice questions, and some reader dissection is a likely, if not anticipated, response. Nonetheless, ample discussion of the answer choices is provided, and serves as a remarkable learning device perfect for group discussions of residents in training. There are some minor problems. For example, in Question 6, a 20-year-old girl has, among other findings, “subtle optic disc edema,” but the answer given is “bilateral retrobulbar neuritis.” Hmm.

Strengths: The material is very balanced, up-to-date, and meticulously illustrated. I predict that many of the illustrations will show up purloined in future basic lectures of Dr. Trobe’s colleagues! That is a compliment. The text is reader-friendly, and the writing style at times verges on conversational (will all readers know what “white coat” hypertension is?). The sixty color fundus photos are carefully selected and of excellent quality. In Chapter 7: “Visual Fields,” the author suggests that field testing “remains deeply flawed, and is rarely used properly.” “Testing is long and boring... results are difficult to interpret...” and that computerized methods “generate a lot of confounding psychophysical ‘noise’.” This said, the reader will find the demonstration of visual fields fully treated; the relevant section forms an excellent fields primer. The index is very thorough, though I suspect not of the author’s construction. Who will look under, for example, “Aging persons,” “Boys,” “Cocktail party,” “Girls. See Females” [do, by all means], “Gotcha,” “Lorenzo’s oil,” “Pizza-pie retinopathy,” and other all-inclusive victimizations of the author’s sensibilities by a distant publishing house indexer?

Weaknesses: Many of the ocular diagrams (i.e., refractive conditions, vitreal disorders, aqueous dynamics in glaucoma), some photos (a bottle of phenylephrine) seem to occupy space unnecessary for ophthalmologists, but perhaps interesting for neurologists. The extraneous items included in the index notwithstanding, it is better to “over-index” than to “under-index”.

Recommended audience: This text will serve well the needs of trainees in neurology and ophthalmology and even medical students. For the former, there is sufficient ophthalmologic material that provides an adequate basic background. For both graduate disciplines, disorders of the afferent visual system are thoroughly covered. The teaching-learning value of the final section, “Problem Cases,” is again worth noting.

Critical appraisal: Altogether a useful, well integrated, cleverly conceived, fully illustrated, and admirable opus from an innovative and skilled educator.

Joel S. Glaser, MD
Bascom Palmer Eye Institute
University of Miami
Miami, FL
Neuro-Ophthalmology: Section 5, Basic and Clinical Science Course

The Foundation of the American Academy of Ophthalmology, San Francisco, CA, 2002. ISBN: 1560552182, Order No.: 415-561-5540, Price: $90.00 for nonmembers, $60.00 for members; Series price: $895.00 for nonmembers, $595.00 for members

Scope: This volume is part of the recently revised edition of the Academy’s Basic and Clinical Science Course designed for residents in ophthalmology. It is a multi-authored, paperback, self-contained practical overview of clinical neuro-ophthalmology that is supposed to encompass all the clinical neuro-ophthalmology an ophthalmology resident needs to know.

Contents: This volume is creatively organized in a symptom-driven approach, designed to focus on how the practicing clinician deals with neuro-ophthalmic signs and symptoms. The authors have attempted to highlight with brief description the more common entities seen in neuro-ophthalmic practice. Emphasis is placed upon the examination and the appropriate use of adjunct testing. The text is readable, clinically relevant, and non-threateningly presented.

The first chapter describes the relevant anatomy that is the framework upon which neuro-ophthalmic understanding is built. The chapter is well illustrated, with color diagrams and schematics. The second chapter deals with neuroimaging in neuro-ophthalmology. It includes helpful tables and practical summaries of when to order, what to order, and how to order such studies. It includes newer and less prevalent techniques such as MRI spectroscopy, PET scanning, SPECT scanning, functional MR, and multifocal ERG. The third and fourth chapters shift emphasis to the patient with decreased vision and lead the reader through a focused approach to differential diagnosis. These chapters are organized by clinical signs—decreased vision with or without a relative afferent defect, with a normal-appearing nerve head, or with disc edema. All the common optic neuropathies are covered (as are less common ones), indeed, some retinal processes that wind up in the neuro-ophthalmologist’s office are discussed, including cone-rod dystrophies, cancer-associated retinopathy, and acute zonal occult outer retinopathy. Ensuing sections describe transient visual loss, disorders of higher cortical dysfunction, nystagmus, anomalous motility, and diplopia. Subsequent chapters walk the reader through pupillary anomalies, facial nerve issues, headache, and functional visual loss. The last chapter summarizes selected common systemic conditions associated with neuro-ophthalmic signs and symptoms, including myasthenia gravis, thyroid orbitopathy, and the neurocutaneous syndromes.

Strengths: This small volume systematically covers the essentials of neuro-ophthalmology that the practitioner need consider. It is remarkable in its breadth. The material is presented practically, speckled with wonderfully illustrated cases, up-to-date scanning, and visual field correlates. The underlying anatomy is emphasized, and treatment possibilities are summarized.

Weaknesses: The authors are such authorities and experts in their field, with so much experience and so much to offer, that occasionally the casual reader will be overwhelmed by detail, especially in the chapters on nystagmus and motility (should “oculomasticatory myorhythmia” have been included?!) Also, some terms may not be familiar to the ophthalmology residents, such as “fascicle” and “long tract sagas.” And yet, one is hard pressed to find lapses in this pithy and paramount overview.

Recommended audience: This volume is designed for the ophthalmology resident and re-certifying ophthalmologist. It will also be useful for neurologists in training.

Critical appraisal: The authors (Newman, Arnold, Friedman, Kline, Rizzo, and O’Connor) are to be congratulated for assembling an innovative, practical, well organized summary of neuro-ophthalmology that is simply and elegantly presented, well written, and highlighted with timely references. This is a readable, one-volume, all-you-need-to-know package of the neuro-ophthalmology seen in community practice, with its underlying basic science. It is fine testimony to the success not only of the authors, but also of the educational program of the American Academy of Ophthalmology.

Barrett Katz, MD, MBA
The George Washington University
Washington, DC

Clinical Neurophysiology of the Vestibular System


Scope: Written by two highly respected contributors to the study of vestibular disease, this book seeks to provide a framework for the understanding of the pathophysiology of vestibular disorders. During the past decade, considerable advances have been reported in the basic scientific principles underlying vestibular disease and their clinical applications. This third edition of a well known textbook has been reorganized and expanded to take into account these developments, and it includes new concepts that explain peripheral transduction and central processing mechanisms within the vestibular system. Following a fundamental dis-
cussion of the anatomy and physiology of the vestibular system, the book focuses on the evaluation and management of the dizzy patient, along with a comprehensive consideration of all aspects of vestibular disease. Overall, there is a structured approach from an explanation of the basic science of vestibular mechanisms through clinical assessment, both bedside and laboratory, of vestibular disorders, and ending with drug and rehabilitation treatment of the vertiginous patient.

Contents: This book is divided into four parts. In part one, there is a detailed explanation of the anatomy and physiology of the vestibular system, both central and peripheral, including an appraisal of the vestibuloocular reflexes and their interaction with other systems. Part two is an evaluation of the dizzy patient, emphasizing the history, bedside examination, laboratory investigations, and clinical assessment of hearing. Part three addresses the diagnosis and management of common neurologic disorders, including infectious disorders, benign positional vertigo, Meniere syndrome, migraine, immune mediated diseases, vascular disorders, tumors, trauma, toxic/metabolic disorders, and developmental and genetic disorders. Part four describes the symptomatic treatment of vertigo, with an evaluation of antiemetic and antivertigo drugs and the rationale for and design of a vestibular exercise program in rehabilitation. The text contains extensive diagrams and tables, along with some imaging and pathology illustrations. At the end of each chapter there is an extensive bibliography.

Strengths: This book provides a comprehensive and up-to-date review of the neurophysiological mechanisms underlying vestibular disorders and their clinical features. The presentation is orderly, readable, and authoritative, while the line diagrams helpfully illustrate underlying morphology and physiological mechanisms. The detailed approaches to the history of the dizzy patient with the bedside and laboratory evaluations are particularly informative. The differential diagnosis of the many causes of dizziness provides an extensive background to the appropriate investigations, while the symptomatic treatment section includes not only drugs and their actions, but also the important issue of vestibular rehabilitation.

Deficiencies: The chapters on diagnosis could have benefited from more extensive and targeted state-of-the-art imaging illustrations (magnetic resonance angiography in vertebrobasilar insufficiency), and the description of the pathology of vestibular disorders might also have been enhanced by further histologic illustrations of, for example, the brain stem. A more extended discussion of the potential management of oscillopsia using, for example, gabapentin, botulinum toxin, or ocular muscle surgery would have been useful.

Recommended audience: This text is primarily aimed at neurotologists but also neurologists, neurosurgeons, and general physicians involved in the care of patients complaining of dizziness. However, neuro-ophthalmologists will also find much of considerable value in this reference text to assist in their understanding, investigation, and management of vestibular disorders.

Critical appraisal: The evaluation and treatment of the dizzy patient presents a difficult and often enigmatic problem. This book provides a thorough explanation of the mechanisms underlying vestibular disorders and a comprehensive review of their evaluation and treatment. It provides an invaluable aid to the assessment of dizziness.

Robert M. McFadzean, MD
Southern General Hospital Institute of Neurological Sciences
Scotland, UK

A Compendium of Degenerative Brain Diseases


Scope: This is a single-authored, soft-cover bird’s eye view monograph addressing neurodegenerative disease.

Contents: This is a concise, focused exposition of the neurophysiology and neuropharmacology of the more common neurodegenerative disorders seen in clinical practice. The text is presented in outline form in three chapters. The opening chapter reviews basic neurophysiology, with an emphasis on the autonomic nervous system and common neurotransmitters. The many excellent diagrams and tables provide a quick and easy reference guide for those preparing for board examinations. The neurotransmitters reviewed in this section include acetylcholine, norepinephrine, dopamine, serotonin, and GABA. Disappointingly, there are no discussions of glutamate, of the NMDA receptor, or of excitotoxicity.

The second chapter reviews in bullet format the common clinical neurodegenerative disorders, including Alzheimer disease, Parkinson disease, Pick disease, Huntington disease, and amyotrophic lateral sclerosis. This section is cogent, well organized, and easy to read. A brief discussion of the pathology, clinical features, etiology, diagnostic criteria, and treatment of each disorder is provided.

The last chapter is lengthy and dedicated to a review of the various medications used to treat degenerative disorders. Medications discussed include the cholinesterase inhibitors, anticholinergics, and dopaminergic agents. This section is in tabular form and includes information about indications, contraindications, dosing, and side effects. The chapter is supplemented by excellent illustrations that depict the mechanisms of action of the described agents.
Strengths: The book provides a concise, easy-to-read discussion of the common neurodegenerative disorders and the standard drugs used to treat them.

Weaknesses: Less common conditions that are relevant to the neuro-opthalmologist, such as progressive supranuclear palsy, cortical basal ganglionic degeneration, and the spinocerebellar ataxias, are not covered. Given the relatively brief description of each entity, evolving subtle issues are omitted, including the importance of tau protein in Alzheimer disease and the role of genetic testing in some of these disorders.

Recommended audience: The book is intended for a wide audience: medical students, residents, and specialists. The former will benefit from it more than the latter. The restricted scope of this monograph will limit its usefulness for those who are ultimately responsible for making decisions about patients with neurodegenerative disease.

Critical appraisal: I enjoyed reading the book and found the information provided to be useful. The arena of neurodegenerative disease is one of intense investigation, and some of the material is dated. Although the text was created for a wide readership, this book will prove to be most useful for neurology and psychiatry residents preparing for board examinations.

Steven L. Galetta, MD
University of Pennsylvania Medical Center
Philadelphia, PA
Downbeat Nystagmus and Dolichoectasia of the Vertebrobasilar Artery

To the Editor:

In 1989, we reviewed the case records and neuroimaging studies of 41 patients with downbeat nystagmus evaluated by the Neuro-ophthalmology Service at the University of Iowa Hospitals and Clinics. We identified two of 41 (5%) patients with downbeat nystagmus of previously undetermined cause who had compression of the caudal brainstem by dolichoectasia of the vertebrobasilar arterial system (1). Based on that report, compression of the caudal brainstem by dolichoectasia of the vertebrobasilar artery has now been included in lists identifying the causes of downbeat nystagmus (2–4). Since our report, others (5,6), including most recently Lee (7) in the September 2001 issue of the Journal of Neuro-Ophthalmology, have identified additional patients with a similar association.

Based on our further experience with additional patients with downbeat nystagmus due to other structural disorders and patients with anatomic compression of the caudal brainstem by dolichoectasia of the vertebrobasilar artery, we now question the validity of the association in all cases for the following reasons:

1. There are patients with anatomic compression and distortion of the caudal brainstem, more severe in degree than the cases referenced in this letter, by other structural disorders that have no downbeat nystagmus (Fig. 1).
2. Similarly, there are patients with anatomic compression and distortion of the caudal brainstem, at least to the degree identified in the referenced cases in this letter, by a dolichoectatic vertebrobasilar artery who have no downbeat nystagmus (Fig. 2).

The anatomic relationship identified in the case reported by Lee (7), and the fact that nystagmus resolved after neurovascular decompression in the case reported by Himi et al. (6), are compelling points in favor of a cause-and-effect relationship between downbeat nystagmus and dolichoectatic arterial compression of the brainstem. Still, we now believe that other variables must exist in addition to anatomic compression to account for the development of downbeat nystagmus. For example, it may be that the specific point of compressive injury, more than compression in general, is important in producing downbeat nystagmus. Perhaps ischemic injury to a specific location is more important than compression in general. Intermittent neurologically isolated downbeat nystagmus has occurred in a patient with intermittent obstruction of the dominant...
vertebral artery (8). A combination of compressive and ischemic injury to a specific location may be required.

Daniel M. Jacobson, MD
Departments of Neurology and Ophthalmology
Marshfield Clinic
Marshfield, Wisconsin

James J. Corbett, MD
Departments of Neurology and Ophthalmology
The University of Mississippi Medical Center
Jackson, Mississippi

Reply:
I thank Drs. Jacobson and Dr. Corbett for their interest in my case report and for raising an interesting question about the pathogenesis and causality in these cases. The authors cite two lines of reasoning for questioning the relationship between dolichoectasia and downbeat nystagmus:

1. Compression and distortion of the caudal brainstem, that is often severe, might have no downbeat nystagmus and
2. Dolichoectatic vertebrobasilar artery cases with compression might not have downbeat nystagmus.

I think that the authors are probably correct that there are probably more factors than just compression alone that may be necessary to manifest symptoms. I would argue, however, that the same two points cited above would apply to all the presumed structural causes of downbeat nystagmus. That is to say, not all Chiari malformation (even severe ones anatomically) produce nystagmus and many are found incidentally. The same could probably be said for hemifacial spasm and dolichoectasia, but we have more data after decompression in these patients to support a causal relationship.

Andrew G. Lee, MD
Department of Ophthalmology and Visual Sciences
University of Iowa Hospitals and Clinics
Iowa City, Iowa

REFERENCES
Walsh and NANOS Meetings Are Successfully Engrafted

Who was minding the neuro-ophthalmology concession in North America from February 9 to 14, 2002? Good question, because over 270 neuro-ophthalmologists gathered during that time at Copper Mountain, Colorado for the first joint Frank B. Walsh (34th) and North American Neuro-Ophthalmology Society (NANOS) (28th) Meetings. A year ago, NANOS members had voted to combine the two meetings so as to conserve on time and travel expenses.

The Walsh meeting, organized by Lanning B. Kline, MD (Birmingham, AL) and William F. Hoyt, MD (San Francisco, CA), featured Peter C. Burger, MD (Baltimore, MD), neuropathology, and Ann G. Osborn, MD (Salt Lake City, UT), neuroradiology, as honored guests. Among the 20 “fascinomas” presented, several got past the audience, and a few even stumped the two experts. The organizers selected four teams of co-moderators, one member of each team having been the fellowship mentor of the other: Shirley H. Wray, MD (Boston, MA) and David Kaufman, MD (East Lansing, MI); Steven E. Feldon, MD (Rochester, NY) and Deborah I. Friedman, MD (Buffalo, NY); James J. Corbett, MD (Jackson, MI) and Daniel E. Jacobson, MD (Marshfield, WI); and William F. Hoyt, MD (San Francisco, CA) and John B. Selhorst, MD (St. Louis, MO). These pairings elicited maudlin expressions of gratitude from the former fellows and melodramatic bursts of pride from the former mentors. Some things were probably left unsaid.

The Walsh meeting segued smoothly into the NANOS meeting, which included 31 platform presentations and 61 posters (see NANOS Abstracts, pp XXX), two high-powered symposia, an expert panel discussion on clinical controversies, an educational skills transfer session on PowerPoint presentations (Edmond J. Fitzgibbon, MD, Bethesda, MD), a practice management session on “making ends meet in academic neuro-ophthalmology” (Richard H. Legge, MD, Omaha, NE), and a biostatistics seminar (Laura J. Balcer, MD, Philadelphia, PA). The two symposia occupied a half-day each. The first covered coagulopathies and vasculopathies, organized by Valerie Biousse, MD (Atlanta, GA), and included John B. Kerrison, MD, PhD (San Antonio, TX), Jeffrey L. Bennett, MD, PhD (Denver, CO), David Lynch, MD, PhD (Philadelphia, PA), and Dr. Stone himself as speakers. As part of his teaching, Dr. Stone challenged the audience to apply newly learned principles of molecular genetics to smoking out bogus manuscript abstracts. Larry Frohman, MD (Newark, NJ) got the highest score and won the prize: a bottle of Chablis.

At the closing banquet, Dr. Balcer announced that the NANOS Board had approved the induction of the following new members: Valerie Biousse, MD (Atlanta, GA), Mohan S. Chandran, MD (San Clara, OH), Steven Covici, MD (Springfield, MA), Ramesh Gopalaswamy, MD (St. Louis, MO), Francis P. Green, MD (Marshfield, MA), Adriana A. Kori, MD (Bend, OR), Jeffrey W. Nichols, MD (Chicago, IL), Lois A. Polatnick, MD (Evanston, IL), Prem S. Subramanian, MD, PhD (Silver Spring, MD), David L. Turok, MD (Buffalo Grove, IL), and Cybele Woon, MD (Columbus, TX). The following members were transferred into NANOS Fellows: Michael C. Brodsky, MD (Little Rock, AK), Lynn K. Gordon, MD, PhD (Los Angeles, CA), Steven R. Hamilton, MD, (Seattle, WA), Sharon J. Johnstone, MD (Phoenix, AZ), David F. Klink, DO (Bethesda, MD), Anil D. Patel, MD (Saskatoon, Saskatchewan), Robert L. Tomsak, MD, PhD (Cleveland, OH), and David A. Weinberg, MD (Burlington, VT). Tulay Kansu, PhD (Iowa City IA) and included John B. Kerrison, MD, PhD (San Antonio, TX), Jeffrey L. Bennett, MD, PhD (Denver, CO), David Lynch, MD, PhD (Philadelphia, PA), and Dr. Stone himself as speakers. As part of his teaching, Dr. Stone challenged the audience to apply newly learned principles of molecular genetics to smoking out bogus manuscript abstracts. Larry Frohman, MD (Newark, NJ) got the highest score and won the prize: a bottle of Chablis.

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Ronald M. Burde, MD (New York, NY) accepts the NANOS Distinguished Service Award.
Thomas J. Carlow, MD (Alburquerque, NM), right, displays the plaque signifying his delivery of the first annual William F. Hoyt Lecture at the Annual Meeting of the American Academy of Ophthalmology, New Orleans, LA, in October 2001. Guess who is pictured on the left?

MD (Ankara, Turkey) was approved as an International Fellow.

The NANOS Distinguished Service Award was given to Ronald M. Burde, MD (New York, NY). In presenting the award on behalf of the NANOS Board, Steven A. Newman, MD (Charlottesville, VA) reminded the audience that Dr. Burde was a founder of the Neuro-ophthalmic Pathology Club (which became the Walsh Society in 1979), the second editor (after J. Lawton Smith, MD) of the Journal of Neuro-Ophthalmology (1994-2001), a mentor to 36 neuro-ophthalmology fellows, and a role model for countless medical students and residents, including Dr. Newman himself. Given in recognition of pivotal contributions to NANOS, this award has been bestowed previously on six individuals: Thomas J. Carlow, MD (Albuquerque, NM), Susan Carlow (Albuquerque, NM), Robert B. Daroff, MD (Cleveland, OH), Joel S. Glaser, MD (Miami, FL), William F. Hoyt, MD (San Francisco, CA), and David T. Knox, MD (Baltimore, MD).

Barrett J. Katz MD (Washington, DC) announced that the first NANOS-sponsored annual William F. Hoyt Lecture at the American Academy of Ophthalmology Annual Meeting was given in 2001 by Thomas J. Carlow, MD (Albuquerque, NM). According to Dr. Katz, Dr. Carlow was selected not only for his many scholarly contributions, but also for being the “driving force behind the NANOS.” The Hoyt Lecture will be published annually in this journal. Dr. Carlow’s lecture, “Ophthalmoplegic Migraine: Is It Really Migraine?” will appear in the September 2002 issue.

The NANOS Young Investigator Award went to Valerie Biousse, MD (Atlanta, GA). A native of Caudean, France, Dr. Biousse originally contemplated a career in physical education, having trained with the French Military Equestrian School while also training in track, hurdles, and long jump. But “while jumping without the horse,” she broke her leg, so she decided to go to medical school, a choice that has led to a stockpile of articles, book chapters, books, and presentations that would make an academic neuro-ophthalmologist 20 years older feel proud. She had decided early in medical school to become a cardiothoracic surgeon and “do lots of heart transplants and create a good artificial heart” until she met Marie-Germaine Bousser, MD (now Professor of Neurology, and Chairman, Department of Neurology, Lariboisiere Hospital, Paris), who steered her toward neuro-ophthalmology. In 1996, Dr. Biousse left her position as staff neurologist at Hotel Dieu in Paris to do a 6-month fellowship in neuro-ophthalmology at Emory University in Atlanta, GA, under the auspices of Nancy J. Newman, MD. Expecting to return to professorial duties in Paris, she was sidetracked by an offer of a faculty position in neuro-ophthalmology at Emory provided she would complete a residency in ophthalmology (which she will do in June of this year).

Dr. Biousse was pleased to discover that teaching has been an important component of her academic progress at Emory, whereas in France she describes teaching more as a “hobby” with no real contribution toward promotion.

Valerie Biousse, MD (Atlanta, GA), center, accepts the 2002 NANOS Young Investigator Award. John B. Selhorst, MD (St. Louis, MO), outgoing NANOS Board chair, left; Neil R. Miller, MD (Baltimore, MD), outgoing NANOS President, right.
Nicholas T. Monsul, MD (Pittsburgh, PA), right, accepts 2002 NANOS Best Resident–Fellow Presentation Award from Neil R. Miller, MD (Baltimore, MD).

Meanwhile, between teaching responsibilities and residency in ophthalmology, she completed the research for which she is being honored this year. It flows from the strength of the molecular genetics program at Emory and specifically Douglas Wallace, PhD, who works exclusively on explicating mitochondrial diseases. Needing someone to look at the eyes of his mitochondrial disease model mice and characterize their phenotypic abnormalities, Dr. Wallace solicited the help of Drs. Newman and Biousse, who have now examined mice from three engineered mice models for evidence of mitochondrial disease with slit lamp biomicroscopy, electrophysiology (ERG and VEP), and histology (light microscopy and EM). These mice show multiple and varied disease manifestations, including congenital cataracts, optic nerve hamartomas, and decreased ERG amplitudes.

The NANOS award for the best resident–fellow presentation at the Annual Meeting went to Nicholas T. Monsul, MD (Pittsburgh, PA). After finishing his ophthalmology residency at Yale, he moved on to a neuroophthalmology fellowship at the Wilmer Institute with Neil Miller, MD. The research for which he is honored deals with axonal regeneration in the optic nerve, conducted under the mentorship of Drs. Paul Hoffman and John Griffin during a 5-month postdoctoral research fellowship at the Johns Hopkins Hospital. His work involves injecting intracocular dibutyryl cyclic AMP into rats either directly before or after optic nerve axotomy and inspecting the nerves at 2 to 8 weeks later. He found that nerves from eyes so injected, before or after the injury, showed axonal regeneration, but control nerves did not.

There is a mystical impulse to Dr. Monsul’s research. When he was 12 years old, a close family member sustained a fall and was rendered paraplegic. He remembers being upset at the time that the spinal cord could not simply regenerate. Since then, he has been on a mission to try to change the remorseless prognosis of similar central nervous system events. He is currently completing an orbit/oculoplastics fellowship under the direction of Kimberly P. Cockerham, MD and John Kennerdell, MD (Pittsburgh, PA).

With these interests, why choose ophthalmology as a career? Because, Dr. Monsul says, “trying to understand the complexity of simply raising your hand is almost beyond comprehension, so if you are going to try to fix an incredibly complex system, chose the simplest part.” At some point, he plans to get back to classic piano, a semiprofessional pursuit in earlier days, and mountain biking (he now wears a helmet).

Lyn A. Sedwick, MD
Orlando, FL

Accreditation of Fellowship Programs Gets a Deferment

The idea of accrediting ophthalmology training programs has been placed on hold following a vote at the
February 2002 meeting of the Association of University Professors of Ophthalmology (AUPO). The AUPO supports the principle of assuring the quality of fellowship training by developing a process of accreditation with accountability, but does not support the current proposal before the American Medical Association's Accreditation Council of Graduate Medical Education (ACGME). The AUPO will coordinate a task force to design an accreditation process, which will consider standard of education, protection of institutional training, public protection, and enforcement.

The history of this issue goes something like this: In the early 1990s, several retina societies and NANOS unsuccessfully petitioned the American Board of Ophthalmology (ABO) to issue ophthalmology subspecialty certifications. (Specialty boards certify physicians as competent; the ACGME accredits training programs as meeting minimum quality standards.) The American Academy of Ophthalmology's (AAO) Board of Councilors then considered the issue of seeking subspecialty accreditation and first voted against it in 1995 and 1996, and then in favor of it in 1997. As a result, the AAO directed the ABO to establish a Fellowship Accreditation Committee to direct ophthalmology subspecialty societies to draft fellowship accreditation requirements. NANOS members approved the accreditation guidelines for neuro-ophthalmology in 1999.

Fellowship program accreditation by the ACGME has the attraction of assuring minimum quality uniform standards. This advantage is counterbalanced by the fact that fellows in accredited programs would have to be paid as house officers rather than as faculty members. Most hospitals would require that fellows be paid based on their years of medical training, namely at the postgraduate year (PGY) 5 or 6 level. In the meantime, the Health Care Financing Administration 1996 capped expenditures for graduate medical education (that means house officers), so that there would be no extra money to cover ophthalmology fellows in accredited programs. To add to the misery: if fellows were to be transformed from faculty members to house officers, they would no longer be able to bill for services, supervise house officers, or take faculty call.

At the February 2002 AUPO meeting, ophthalmology program directors got a taste of the potential problems of fellowship accreditation from Steven Nestler, PhD, Executive Director of the ACGME's Residency Review Program.
Mentor/mentee pair (originally University of Iowa) James J. Corbett, MD (Jackson, MS), right, and Daniel M. Jacobson, MD (Marshfield, WI).

Suzanne C. Berry, NANOS Administrative Director, left, with Thomas J. Carlow, MD (Albuquerque, NM) at the poster session.

Committee for Ophthalmology and Orthopedic Surgery, who reported the experience of orthopedic surgery, which achieved permission to accredit eight subspecialty programs in 1985. Only one program, hand surgery, has a certification process. Of 375 programs, 175 programs are accredited, most in academic institutions. The major points from Dr. Nestler's presentation were: 1) accreditation is a long process and that many orthopedic programs have not chosen to become accredited for a variety of reasons, and 2) the ACGME would not support accreditation for ophthalmic programs.

Mentor/mentee pair (originally Michigan State University) David Kaufman, DO (East Lansing, MI), right, and Michael S. Vaphiades, DO (Little Rock, AK).

William F. Hoyt, MD (San Francisco, CA) points out an interesting item on the poster of Grace W. Kao, MD, MPH (Orange, CA).
The NANOS Accreditation Committee (John L. Keltner, MD, Mark L. Moster, MD, Steve A. Newman, MD, and Ralph A. Sawyer, MD) rethought the pros and cons of neuro-ophthalmology fellowship accreditation, having polled NANOS fellowship directors and discovered that a majority could not afford accredited fellows. At the February 2002 AUPO meeting, most of the program directors in other ophthalmic subspecialties had come to the same conclusion and voted to find another way to accredit fellows that they could afford. The NANOS Accreditation Committee is looking into the feasibility of accrediting programs based on a NANOS (rather than ACGME) monitoring system that would be based on NANOS-approved standards. The committee will be anxious to see what the AUPO develops. A report is expected at the next NANOS meeting at Snowbird, Utah, in February 2003. Stay tuned.

John L. Keltner, MD  
Davis, CA

Ralph A. Sawyer, MD  
North Potomac, MD
Editor's Note: The abstracts from platform and poster presentations at the annual winter North American Neuro-Ophthalmology Society (NANOS) meeting of that year always appear in the June issue of the Journal of Neuro-Ophthalmology. Platform presentations appear first, followed by poster presentations. Only the first author’s name is listed.


PLATFORM PRESENTATIONS

Endocrinologic Abnormalities in Idiopathic Intracranial Hypertension (Pseudotumor Cerebri) in Men
First Author: Andrew Lee, MD, Iowa City, Iowa

Background: Idiopathic intracranial hypertension (IIH) is uncommon in men. Endocrinologic abnormalities have been reported in some cases of IIH.

Methods: We identified cases of IIH in men and performed endocrinologic testing in 8 patients including serum free T4, thyroid stimulating hormone (TSH), estradiol, Follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone, sex hormone binding globulin, free testosterone, and percentage free testosterone.

Results: Two patients had abnormal estradiol, four had abnormal FSH and LH, and seven had low testosterone levels.

Conclusion: Endocrinologic abnormalities in male patients with IIH may be a clue to the pathogenesis of the disorder.

Perceptual Correlates Of The Human Dorsal Light Reflex
First Author: Michael Brodsky, MD, Little Rock, Arkansas

Background: Dissociated vertical divergence (DVD) has been attributed to a primitive dorsal light reflex that emerges in humans when single binocular vision is precluded in infancy. If this is the case, then DVD should be associated with a subjective sensation of tilt.

Methods: Alternate cover testing was performed in 9 patients with dissociated vertical divergence, who viewed a vertical object held in the sagittal plane.

Results: Alternate occlusion disclosed a tilt in the subjective visual vertical in 8 of the 9 patients with DVD. Upon occlusion of the fixating eye, the upper pole of a vertical object held in the sagittal plane was perceived as initially tilted toward the side of the covered eye. The ensuing cyclovertical divergence movement served to restore normal vertical orientation to the visual environment.

Conclusions: This sequence of perceptual alterations supports the notion that DVD is a human dorsal light reflex, which restores vertical orientation when unequal binocular visual input produces a visual tilt in the roll plane.

Cerebral Venous Pressure Studies in Idiopathic Intracranial Hypertension
First Author: John King, MD, Melbourne, Australia

Objective: To measure cerebral venous sinus pressures in patients with idiopathic intracranial hypertension (IIH), and to study the effect of simultaneously lowering intracranial pressure by cervical puncture.

Methods: Twenty-one patients with IIH and 10 patients with other illnesses underwent cerebral venography and manometry by the transfemoral route. In 11 patients, 8 with IIH, a second neuroradiologist performed a C1–2 puncture immediately after the initial measurements. The intracranial pressure was lowered by removal of 20–25 ml of CSF and the venous pressure measurements were repeated.

Results: Nineteen of 21 cases with IIH showed a pressure drop of between 9 and 46 mm Hg across the transverse sinuses (TS). Of the 10 patients with diseases other than IIH, 7 had normal studies, but 3 showed the same pressure drop across the TS. 2 had diabetes with unilateral TS thrombosis and one had minocycline-induced intracranial hypertension. Lowering the intracranial pressure by C1–2 puncture abolished the pressure drop across the TS.

Conclusion: Cerebral venous hypertension is common in IIH but can be relieved by lowering intracranial pressure. It is suggested that the obstruction to venous outflow is
Comparison of Opening Pressures During Lumbar Puncture in the Prone and Lateral Positions in Patients with Idiopathic Intracranial Hypertension

First Author: Daniel Jacobson, MD, Marshfield, Wisconsin

Background: Performing LP in the office in some patients with IIH is difficult due to their body habitus. Accordingly, radiologists are often asked to perform the procedure using fluoroscopic guidance. During this procedure, the OP is typically recorded in the prone position. But, it is not known whether the OP obtained in the prone position is comparable to that obtained in the lateral decubitus position.

Objective: To compare the opening pressure (OP) obtained during lumbar puncture (LP) in the prone and lateral positions in patients with idiopathic intracranial hypertension (IIH).

Methods: Following informed consent, consecutive patients with suspected or confirmed IIH who required LP for diagnostic confirmation or management were prospectively enrolled. The procedures were performed using fluoroscopic guidance. The OP was first recorded in the prone position. After the patient was then placed in the lateral position with their legs fully extended, the OP was again recorded. The Wilcoxon signed rank test (two-tailed) was used to determine whether there was a significant difference between the OP recorded in these two positions. The Spearman rank correlation test (two-tailed) was used to determine whether there was a relationship between body mass index (BMI) and OP.

Results: Of the nine patients enrolled thus far, two were excluded: one because she probably did not have IIH and one because she refused LP. Of the remaining seven patients, all were women and ranged in age from 18 to 39 years (median age, 25 years) and had BMI that ranged from 22 to 47 kg/m² (median BMI, 33 kg/m²). The OP in the prone position ranged from 240 to 430 mmHgO (median, 340 mmHgO), while that recorded in the lateral position ranged from 190 to 420 mmHgO (median, 320 mmHgO) (p = 0.30). The pressure was higher in the prone position than in the lateral position in five of the patients by an average of 51 mmHgO, and was higher in the lateral position than in the prone position in two of the patients by an average of 35 mmHgO. While a weak inverse relationship between BMI and OP in the prone (r = -0.40, p = 0.40) and lateral (r = -0.31, P = 0.50) position was suggested, the results were not significant.

Conclusions: As a group, there was no significant difference in the OP in the prone and lateral positions. But, the small number of patients and substantial overlap of values in these two groups limits the power of this conclusion. Accordingly, although using the prone measurement for patients may be acceptable when the value is markedly elevated, we do not recommend relying on this for diagnostic purposes if the prone value is near the normal limit, either above or below it.

Radiosurgery and Optic Nerve Tolerance: Fact and Fiction

First Author: Scott Stafford, MD, Rochester, Minnesota

Background: The tolerance of the ON to single fraction radiation is frequently quoted as 8 Gy (1,5) However, this threshold dose has been questioned and is thought to be overly conservative based on more recent data utilizing improved neuroimaging and dose-planning software (2,3,4). Objective: To evaluate the radiation tolerance of the optic nerve (ON) after radiosurgery.

Methods: We reviewed the dose plans of 218 Gamma Knife® procedures (215 patients) for patients with benign tumors of the sellar and parasellar region (meningiomas, n = 122; pituitary adenomas, n = 89; craniopharyngiomas, n = 7 patients) and calculated the maximum radiation dose to the ON after radiosurgery. Median patient age was 52 years. Previous surgery or radiation therapy (mean dose, 50.2 Gy) was performed in 75 (35%) and 24 (11%) patients, respectively. The median prescription volume 6.3cc (range, 0.09–30.4cc); the median prescription dose was 18 Gy (range, 12–30). Median clinical follow-up was 40 months (range, 4–115) with 94% of patients having more than 9 months of follow-up.

Results: The median maximum radiation dose to the ON was 10 Gy (range, 0.4–16.0). Four optic nerve complications (1.8%) occurred at a median of 31 months after the last radiosurgical procedure.

Conclusions: Visual decline was noted in only three of 156 patients (1.9%) receiving 8 Gy or more to the ON and may be attributed to RS in one patient receiving 7 Gy to the ON. Optic nerve toxicity after contemporary radiosurgery is rare, and the risk is likely increased for patients receiving prior radiation to that region.

References:
Toxoplasmic Anterior Optic Neuropathy

First Author: James Banta, MD, Miami, Florida

Objective: To describe clinical findings and course of toxoplasmic anterior optic neuropathy and to differentiate primary and secondary involvement.

Methods: Observational case series

Results: Toxoplasmic anterior optic neuropathy was divided into two types. Type I was defined as secondary infectious involvement of the optic nerve head from an adjacent focus of chorioretinitis that resolved with chorioretinal scarring. Type II was defined as primary involvement of the optic nerve head that resolved without chorioretinal scarring. Visual acuity improved after treatment in both Type I and Type II, however the visual prognosis was worse in Type I patients due to macular involvement. Eighty-three percent of Type II patients had a final visual acuity equal or better than 20/25 compared with 50% of Type I patients. Visual field defects were present in all patients, most frequently arcuate or altitudinal (62%). Delay in diagnosis was common (54%), especially in Type II patients (71%). Vitreous inflammation was absent on the initial examination in 31% of patients.

Conclusions: Toxoplasmic anterior optic neuropathy is an uncommon manifestation of ocular toxoplasmosis. Delays in diagnosis are common because of frequent lack of typical chorioretinitis or vitreous inflammation. Adjacent macular involvement strongly influences visual outcome.

Symptomatic Chiari I Malformation

First Author: Kimberly Cockerham, MD, Pittsburgh, Pennsylvania

Background: Chiari I malformation (ACM) refers to the descent of the cerebellar tonsils at least 5mm below the foramen magnum. ACM patients often suffer symptoms of dizziness, imbalance, headache, retro-orbital pressure, transient visual obscurations and neck pain. Intracranial noises are also often present. The symptoms are very similar to patients with idiopathic intracranial hypertension but ACM patients do not typically develop disc edema.

Objective: To perform complete neuro-ophthalmic evaluations in patients with symptomatic ACM.

Methods: Prospective case series of 32 patients with significant cerebellar tonsillar descent on sagittal magnetic resonance imaging. A complete neuro-ophthalmic examination was performed to include visual field testing and HRT nerve fiber analysis.

Results: 6 men and 26 women were evaluated. The mean age was 37 years (range 8–58). The most common visual complaint was transient visual obscurations lasting seconds (n = 30). Pain or fullness behind the eyes was present in 29 patients.Persistently decreased vision or double vision was not present in any of those examined. Afferent function was normal including visual field testing. Fundus examination was remarkable for the lack of venous pulsations in 24 patients (75%). Mild hyperemia with telangiectatic vessels was noted in 3 patients. Disc edema was not present. No patients demonstrated cranial nerve deficits or nystagmus. In four patients seen following ACM decompression surgery who noted resolution of symptoms, normal spontaneous venous pulsations were present. In 3 patients where ACM decompression surgery failed to provide symptomatic improvement, spontaneous venous pulsations were not noted following surgical intervention.

Conclusions: Patients with symptomatic Arnold Chiari malformation have a higher prevalence of dampened spontaneous venous pulsations. Successful surgical decompression can result in improved symptoms and return of spontaneous pulsations. Lack of spontaneous venous pulsations following ACM decompression may predict procedure failure.

Autoimmune-Related Retinopathy and Optic Neuropathy (ARRON) Syndrome

First Author: John Keltner, MD, Sacramento, California

Objective: To evaluate patients who have unexplained visual loss without evidence of malignancy whose clinical and immunologic profiles are consistent with autoimmune-related retinopathy and optic neuropathy (ARRON) syndrome.

Methods: The clinical information and immunologic findings from U.C. Davis and other referred patients were tabulated and analyzed.

Results: This study included 12 ARRON patients, 8 women and 4 men, with the average age of presentation to U.C. Davis Ophthalmology Department at 50 years (range 37 to 75). Visual loss in these patients was frequently asymmetric. Visual acuity varied from 20/20 to no light perception (NLP). Visual field loss consisted of mild to severe loss with generalized peripheral constriction. Some patients demonstrated normal field in one eye with severe mean deviation loss or NLP in the other eye. Fundus findings showed 11 of the 12 patients had optic nerve atrophy and 8 of the 12 patients had non-specific retinal changes except
for blood vessel attenuation in 3 patients. ERG abnormalities were present in 10 out of 11 patients. Evaluation for cancer was negative in all patients. Systemic immunologic diseases were present in 8 out of 12 patients, which included systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), hyperthyroidism, hypothyroidism, celiac sprue, Sjögren’s disease, psoriatic arthritis, and idiopathic thrombocytopenic purpura (ITP). Immunologic evaluation on both Western blot and immunohistochemistry demonstrated a variety of autoimmune reactions to retina and optic nerve. Visual function in 7 out of 12 patients were stabilized with immunomodulation, which included some combination of prednisone, other immunosuppressive therapy, IVIG, and/or plasma exchange.

Conclusions: The autoimmune-related retinopathy and optic neuropathy (ARRON) syndrome represents a diverse group of patients without cancer, but have visual loss and may exhibit antibodies to retina and optic nerve. These patients frequently have other autoimmune diseases and their visual loss may respond to steroid and other immunomodulators.

The Effect of Decreased Visual Acuity on Clinical Color Vision Tests

First Author: Timothy McCulley, MD, Cincinnati, Ohio

Background: In patients with poor visual acuity, it is not always clear whether errors on color vision testing are due to an abnormality in color vision or inadequate acuity.

Objective: To evaluate the effect of decreased visual acuity on clinical color vision tests.

Methods: The ODs of 12 healthy subjects (11 females, 1 male, mean age 38, range 20 to 61) with no history of color vision abnormality and normal visual acuity were fogged with plus lenses at the phoropter to visual acuity of logMAR 1.88 (20/1500) at near and assessed with Farnsworth D-15 hue discrimination test, Ishihara color plates, and Hardy-Rand-Rittler (HRR) color plates. Subjects were similarly tested at progressively lesser degrees of fogging, at 0.1 logMAR intervals, up to acuity logMAR 0.67 (20/94) and at baseline, logMAR 0 (20/20). For all levels of visual acuity the mean number of errors made with each color vision test was compared with baseline using the paired t test. To compare examination devices, for each subject the worst visual acuity that the number of errors did not differ from baseline was determined for each color vision test. These acuities were averaged for each color vision test and compared using repeated measures analysis of variance.

Results: The number of errors on color vision testing did not significantly differ from baseline, using the cutoff p = 0.05, up to including visual acuities logMAR 1.57 (20/750) on D-15 panel, L.27 (20/375) on HRR plates, and 0.88 (20/150) on Ishihara plates. The measures analysis of variance on the most decreased unaffected acuity was highly significant (p < 0.001). All three-color vision tests were significantly different from each other (all p < 0.005).

Conclusions: Of the three-color vision assessment techniques, Ishihara plate testing was most dependent and the Farnsworth Panel D-15 was least dependent on good visual acuity. Color vision testing was accurate up to and including acuity of logMAR 1.57 (20/750) with the D-15 panel, 1.27 (20/375) with HRR plates, and 0.88 (20/150) with Ishihara plates.

Successful Treatment with Acetazolamide in Pregnant Women with Pseudotumor Cerebri

First Author: Misha Pless, MD, Pittsburgh, PA

Objective: To report 6 patients who were treated with acetazolamide during pregnancy for the diagnosis of pseudotumor cerebri (PTC). Specifically to identify potential teratogenic effects of Diamox and to evaluate the settings where acetazolamide treatment is appropriate in the setting of pregnancy.

Methods: A retrospective chart review of 171 patients treated at the Neuro-ophthalmology unit of the University of Pittsburgh's Eye and Ear Institute between 1996 and 2001 with the diagnosis PTC identified 6 patients who received acetazolamide during pregnancy.

Results: Between July 1996 and December 2000, 171 patients were diagnosed with PTC at the University of Pittsburgh's Eye and Ear Institute. In this database 6 women were identified who were either pregnant at the time of diagnosis or became pregnant during treatment with acetazolamide (age range 20–32). The study was designed to prospectively follow the 6 patients into completion of pregnancy and beyond delivery. Their infants were examined by pediatricians in the standard fashion. All 6 patients had moderate or severe PTC with Frisen grade III-V papilledema at presentation to neuro-ophthalmic care (LP opening pressure 32 to > 55 cm CSF). All patients had mild to moderate visual function and field compromise. All 6 individuals were given both medical and surgical choices for the treatment of PTC. All patients understood the reported teratogenic effects of acetazolamide. Two patients became pregnant while being treated with acetazolamide 1 gm/d while the remaining 4 women received the diagnosis of PTC and began treatment within the first trimester of pregnancy (range 8–14 weeks) with similar dosing. One child was born at 32 weeks gestation secondary to premature rupture of membranes. None of the 6 infants had any
Video versus Graphic Representation of the Swinging Flashlight Test: Enhancing Examiner Accuracy in the Detection of Afferent Pupillary Defects

First Author: Shane Kim, MD, Philadelphia, PA

Background: Video documentation and graphic representation of the swinging flashlight test (SFT) have never been systematically tested as a method to enhance observers' ability to detect afferent pupillary defects (APDs).

Objective: To compare the ability of different examiners to identify and quantify APDs presented as videos and as graphs (pupillary diameter versus time) of the SFT.

Methods: Video recordings and graphs (N = 60) of the SFT in normals and in patients with APDs: mild (< 0.6 log unit), moderate (0.6-0.9 log unit), or severe (> 0.9 log unit) were presented to ophthalmic caregivers (N = 21) divided into 3 groups: medical students and technicians (MST), residents (R), and neuro-ophthalmologists (N). For each video or graph, the examiners made a diagnosis of normal, mild, moderate, or severe APD. A scoring system was developed to assess accuracy.

Results: In all groups, the mean accuracy score using graphs was higher than that of videos (p < 0.001). Using videos, the groups recognized moderate APDs 42.9% (MST), 66.4% (R), and 88.1% (N) of the time. Using graphs, identification of moderate APDs improved in all groups: 64.3% (MST), 88.6% (R), and 96.4% (N). For videos, a gross error (failing to detect a severe APD) was made 16.7% (MST), 5% (R), and 0% (N) of the time. For graphs, a gross error was made 26.7% (MST), 1.7% (R), and 0% (N) of the time.

Conclusions: There was a direct correlation between the experience of the examiner, and the ability to identify moderate and severe APDs. The ability to detect moderate APDs increased in all groups when response curves were used. The disparity between the accuracy of experts and nonexperts in identifying moderate APDs decreased when graphs were used, suggesting that graphic representation of the SFT obtained through pupillography may be an important diagnostic tool.

The Role of Unilateral Temporal Artery Biopsy

First Author: Nicholas Volpe, MD, Philadelphia, Pennsylvania

Background: The routine use of bilateral temporal artery biopsy (TAB) to exclude giant cell arteritis (GCA) has been suggested because of a small percentage of discordant results in bilateral biopsies.

Objective: To examine the role of unilateral TAB in suspected GCA.

Methods: We identified 181 patients who underwent TAB (1990–2001). Follow-up information (obtained by telephone or record review) for patients with unilateral negative TAB was reviewed for potential adverse outcomes due to missed or delayed diagnoses of GCA. Patients' presenting signs, symptoms and laboratory values were recorded. Comparisons of clinical profiles between subsets of patients were performed using Fisher exact tests.

Results: Follow-up information was available for 88 of 102 patients (86%) who had unilateral negative biopsies. One patient of 88 (1%) had a subsequent positive contralateral TAB; no adverse outcomes occurred for this patient or for any other patients with unilateral negative TAB. Compared with patients who had unilateral positive or who underwent bilateral TAB (n = 78), those who had unilateral negative TAB (n = 88) had a significantly lower prevalence of jaw claudication (p = 0.005). Compared with patients diagnosed with GCA (n = 39), those with unilateral negative TAB (n = 88) had significantly lower frequencies of jaw claudication (p = 0.001), "chalky white" optic disc appearance (p = 0.002) and fever (p < 0.0001). The most common indications for biopsy in patients with unilateral negative TAB were elevated erythrocyte sedimentation rate (ESR) (74%), headache (69%), visual symptoms (58%), and ophthalmic signs (52%).

Conclusions: Unilateral TAB was associated with a low frequency (1%) of subsequent positive contralateral TAB, and was not associated with adverse visual or neurologic outcomes for any patient. This suggests that a unilateral TAB is sufficient to exclude a diagnosis of GCA in populations for which clinical suspicion is low. Jaw claudication, "chalky white" optic disc appearance, and fever should raise suspicion for a diagnosis of GCA.
The Multifocal Electroretinogram in a Neuro-ophthalmology Practice

First Author: Candice Chen, MD, New York, New York

Objective: To investigate the use of the multifocal electroretinogram (mFERG) in a neuro-ophthalmology practice.

Methods: Between March 1999 and November, 2001, 71 patients were referred from a single neuro-ophthalmology practice for mFERG testing. Each patient had a mFERG recorded with a bipolar Burian-Allen contact lens electrode or a DTL electrode after the pupil was dilated with 1% tropicamide. The mFERGs were recorded using equipment and software from EDI. The display, 50° in diameter, consisted of 103-scaled hexagons. One 7-minute run was recorded from OU. Amplitudes and latencies were examined with the VERIS software and programs written in MATLAB.

Results: Sixty-one of the patients were tested for diagnostic purposes: to rule out the retina as the site of disease (ROR, n = 39); to distinguish between diseases (2D, n = 9); to rule out functional or non-organic causes (F, n = 7); and to follow progression of a retinal disease (P, n = 6). The remaining 10 were part of ongoing studies (e.g. the effects of ION and of the papillorenal syndrome on the mERG). In 3 of the 61 patients seen to aid in the diagnosis, we were unable to obtain usable records due to poor fixation, technical problems or the patient’s inability to tolerate the test. Of the remaining 58 patients, the mFERG was abnormal in 14 of the 37 ROR patients, 6 of 9 the 2D patients, and none of the 7 F patients. Five of the 6 progression patients could be followed with the mFERG. The sixth progression patient was unable to tolerate the test.

Conclusions: The mFERG aided in the diagnosis and the planning of treatment of most of patients. Of particular importance was the mFERG’s ability to distinguish diseases of the retina (pre-ganglion cells) from diseases of the ganglion cells and the optic nerve.

A Functional MRI Study of Benign Essential Blepharospasm

First Author: Robert Baker, MD, Lexington, Kentucky

Background: Our laboratory has focused on the etiology and treatment of BEB. We now apply the modality of FMRI to this effort.

Objectives: We sought differences in blink induced brain activation patterns between 5 BEB patients and 5 normals.

Methods: Blood oxygen level-dependent intensity images were collected as 16, 8mm thick slices using a t2-star gradient echo epi sequence, co-registered with anatomic images. Spatially normalized and isotropically blurred activation maps for each subject were combined within BEB and controls groups to generate maps of intersubject mean fractional signal change.

Results: Greater activation during spontaneous and voluntary blinking was seen in BEB compared with controls in the anterior visual cortex, primary motor cortex, central region of the thalamus, and superior cerebellum. Differences were greatest for voluntary blinking.

Conclusions: The activation observed might represent a hyperactive cortical circuit linking visual cortex, limbic system, supplementary motor cortex, cerebellum, and subnuclear motor pathways innervating the periorbital muscles.

Field Investigation in Brazil of a Giant Pedigree of Leber’s Hereditary Optic Neuropathy

First Author: Alfredo Sadun, MD, PhD, Los Angeles, California

Objective: To travel to rural Brazil to find as many members of a previously unstudied pedigree known to have Leber’s hereditary optic neuropathy (LHON). Further, to conduct extensive epidemiological, neuro-ophthalmological, psychophysical and blood examinations to conduct multi-variant analysis on epigenetic factors and gene linkage analysis.

Background: A mother from rural Brazil had a 14-year-old son go blind in one eye. Her brothers had also gone blind as young adults. Molecular analysis of blood samples showed that all 4 individuals had LHON, 11778, homoplasmic, J-haplotype.

Methods: Investigators from the University of Sao Paulo traveled to the remote city of Colatina, Brazil, where they were joined by an international team of investigators. An extensive questionnaire, previously used on a large LHON pedigree, was further adapted for local conditions and translated into Portuguese. The full LHON pedigree consisted of approximately 300 members. These patients moved through 6 stations: 1) epidemiological interview; 2) blood drawing for molecular analysis, biochemical studies, and gene linkage analysis; 3) comprehensive neuro-ophthalmological examination; 4) psychophysical studies including contrast sensitivity, color vision, and threshold Amsler grid testing; 5) Humphrey visual field 30-2 perimetry; and 6) fundus photography.

Results: A total of 295 patients were found to be members of this large pedigree. 273 patients were located and examined in Brazil and 4 others in the U.S. The pedigree began in...
The use of low-contrast Sloan letter chart testing as a candidate visual outcome measure for the Multiple Sclerosis Functional Composite (MSFC) was studied in a sub-study of an randomized clinical trial. The study included cross-sectional and functional composite testing of 277 members of a 295-member pedigree with LHON 11778. The analysis of environmental risk factors and genetic linkage analysis of the nuclear DNA will help elucidate the question of why only a fraction of individuals with Leber's disease express the disease. The genetic and epigenetic factors that may modulate the threshold of expression of LHON have yet to be elucidated. Furthermore, this fully described database may provide an excellent opportunity for future clinical trials of any purported neuroprotective agent.

Conclusions: Low-contrast Sloan letter chart testing captures aspects of neurologic impairment in MS not entirely captured by high-contrast visual acuity, EDSS, or MSFC scores, and demonstrates excellent potential as a candidate MSFC visual component.

Hering is Hooked by Monocular Adaptation of the VOR; Lessons from Sixth Nerve Palsy

First Author: Agnes Wong, MD, St. Louis, Missouri

Background: The effects of paralytic strabismus on the vestibulo-ocular reflex (VOR) have not been systematically investigated.

Objective: To analyze the horizontal VOR in patients with unilateral peripheral sixth nerve palsy.

Methods: Twenty-one patients (6 severe, 7 moderate, 8 mild) and 15 normal subjects were studied. Subjects underwent sinusoidal ± 10 deg head on body rotations in yaw at approximately 0.5 and 2 Hz. Eye movement recordings were performed using magnetic scleral search coils in OU during monocular viewing in light and in darkness.

Results: In all patients, horizontal VOR gains in darkness were decreased in the paretic eye in both abduction and adduction, but remained normal in the non-paretic eye in both directions. In light, horizontal visually enhanced VOR (VVOR) gains were normal in both eyes in moderate and mild palsies. In severe palsies, horizontal VVOR gains remained low in the paretic eye during viewing with either eye, while those in the non-paretic eye were higher than normal when the paretic eye viewed.

Conclusions: In darkness, horizontal VOR gains are reduced during abduction of the paretic eye in all patients, as anticipated in sixth nerve palsy. Gains are also reduced during adduction of the paretic eye, suggesting that innervation to the medial rectus has changed. After severe palsy, vision does not increase abducting or adducting horizontal VVOR gains to normal in the paretic eye, but causes secondary increase in VVOR gains to values above unity in the non-paretic eye, when the paretic eye fixates. In mild and moderate palsies, vision enhances the VOR in the paretic eye but does not increase adducting or abducting horizontal VVOR gains to normal in the non-paretic eye, but causes no change in the non-paretic eye, suggesting a monocular readjustment of innervation selectively to the paretic eye. This monocular adaptation in the VOR of the paretic eye was significant to a modest-moderate degree, supporting a potential role for LCSLC testing in MS. Median binocular Snellen acuities were 20/20 (20/16-20/100) in both studies. Among 165 visual outcome measures in the Penn MS Study (including high-contrast visual acuity), LCSLC scores best-distinguished MS patients from age-matched controls on the basis of visual function, even following detailed refractions (p < 0.006, logistic regression analysis).

Conclusions: LCSLC testing captures aspects of neurologic impairment in MS not entirely captured by high-contrast visual acuity, EDSS, or MSFC scores, and demonstrates excellent potential as a candidate MSFC visual component.
THE Retinal Nerve Fiber Layer in Patients with Compressive Optic Neuropathy

First Author: Julie Falardeau, MD, Iowa City, Iowa

Background: Currently, there is no means available to assess visual prognosis of patients with compressive optic neuropathy who are being evaluated for treatment except for degree of pallor of the optic nerve. The number of surviving, viable ganglion cell axons might be related to the thickness of the retinal nerve fiber layer and could be used to assess reversibility of visual field loss.

The Effect of Fibrous Dysplasia on the Optic Nerve Canal and Vision

First Author: Edmond FitzGibbon, MD, Bethesda, Maryland

Background: In fibrous dysplasia of bone (FD), fibro-osseous tissue replaces normal bone. The anterior cranial base is frequently involved in the polyostotic form. The optic nerve passing through the sphenoid wing is often found to be partially or completely encased by FD on CT. Some surgeons have advocated prophylactic optic nerve decompression to preserve sight in these patients.

Objectives: The purpose of this study was to: 1) correlate the CT findings and neuro-ophthalmic exams in FD patients, 2) quantitate the CT findings and optic canal parameters, and 3) establish evidence-based management for optic nerves encased with FD.

Methods: 38 patients with FD (age range 4–59) were included in this study. Inclusion criteria included FD of the sphenoid wing. Exclusion criteria included prior optic nerve decompression procedure or treatment with bisphosphonate therapy. The CT images were reformatted through the optic canal and involvement, height, and width were measured by a masked neuro-radiologist who also measured CTs of age- and sex-matched controls. Visual acuity, Humphrey visual fields, Ishihara color test and funduscopic exams were performed by a neuro-ophthalmologist masked to the CT findings.

Results: Of the 68 involved canals, 70.6% had circumferential canal involvement and 29.4% had partial involvement. 5 patients had acuity or color vision abnormalities attributable to red green color blindness or amblyopia. Of the 38 patients, only one had vision loss in one eye from optic neuropathy.

Conclusions: The majority (97%) of the FD patients with optic nerve involvement had normal eye exams. Therefore, prophylactic optic nerve decompression is not recommended based on radiographic findings alone since they do not correlate with vision loss.

Prognostic Value of Optical Coherence Tomography of THE Retinal Nerve Fiber Layer in Patients with Compressive Optic Neuropathy

First Author: Edmond FitzGibbon, MD, Bethesda, Maryland

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Conclusions: The majority (97%) of the FD patients with optic nerve involvement had normal eye exams. Therefore, prophylactic optic nerve decompression is not recommended based on radiographic findings alone since they do not correlate with vision loss.

A Spatial Working Memory Component to Visuospatial Neglect

First Author: Christopher Kennard, MD, London, United Kingdom

Background: In the hemispatial neglect syndrome, usually due to a right inferior parietal lesion, patients tend to only search the ipsilateral half of the visual scene. Several lines of research suggest that multiple components underlie the neglect syndrome but a common theme has been a bias of attention. In an experimental paradigm using a visual search task a single case study indicated impaired spatial working memory (SWM) across saccades contributing to abnormal search in neglect.

Objective: To determine the prevalence of any such trans-saccadic spatial working memory deficit in a population of neglect patients using a multi-target search task.

Methods: Sixteen patients with left neglect due to right-hemisphere infarction or hemorrhage were studied and their performance was compared with a group of 15 healthy aged-matched volunteers. Subjects viewed a computer monitor showing a series of search displays comprising 19 targets (T's) embedded amongst 44 distracters (L's). The task a single case study indicated impaired spatial working memory (SWM) across saccades contributing to abnormal search in neglect.

Results: All neglect patients found significantly fewer targets on the left half of the screen than the right. The neglect group had a significantly higher refixation rate than the control group. Eleven of the 16 patients had refixation rates beyond the upper 95% confidence limit for normal subjects indicating an impairment in SWM.

Conclusions: In this visual search task many of the neglect patients erroneously judged previously located targets to be new discoveries, significantly more often than healthy individuals. An impairment in keeping track of search locations may, therefore, be a relatively common component of the neglect syndrome and may contribute to the severity of the condition.
Objectives: To assess the prognostic value of optical coherence tomography (OCT) of the retinal nerve fiber layer in predicting visual recovery in patients with compressive optic neuropathy and visual field loss.

Methods: 15 eyes (11 patients) with compressive optic neuropathy from meningioma of the optic nerve (3), intracranial meningioma (1), pituitary tumor (3), Grave’s (3) and ophthalmic artery aneurysm were evaluated by OCT and visual field testing (Humphrey SITA 24-2). Patients were retested after decompression or radiation. The average retinal nerve fiber layer thickness was compared in eyes that improved in mean deviation after treatment with those that did not.

Results: The average retinal nerve fiber layer of 11 eyes that improved was significantly (P < 0.006) thicker (mean = 120.9 μm) compared with 4 eyes that did not (mean = 71.7 μm). A significant correlation was found between the average thickness of the retinal nerve fiber layer and the post-treatment mean deviation of the Humphrey visual field (Pearson correlation coefficient = 0.658 p < 0.01). No significant correlation was found between the average retinal nerve fiber layer thickness and the pre-treatment mean deviation.

Conclusions: Measurement of retinal nerve fiber layer thickness by Optical Coherence Tomography provides a new means of assessing the reversibility of visual loss and prognosis in patients with compressive optic neuropathy.

Role of Cyclic AMP in Axon Regeneration in the Mammalian CNS

First Author: Paul Hoffman, MD, PhD, Baltimore, Maryland

Background: The lack of effective axon regeneration in the central nervous system (CNS) of adult mammals reflects the presence of molecules associated with CNS myelin that are potential inhibitors of axon elongation. The actual ability of these molecules to block regeneration depends on the intrinsic growth state of neurons. The high intrinsic growth state of developing neurons allows axon regeneration in the CNS. This capacity is lost as the intrinsic growth state declines during postnatal development. Changes in the intrinsic growth state correlate with alterations in neuronal cyclic AMP (cAMP) levels.

Objectives: To determine whether dibutyryl cAMP (db cAMP), a membrane-permeable cAMP analogue, can promote the regeneration of sensory axons in the dorsal columns of the spinal cord.

Methods: Sensory neurons in adult rats were exposed to db cAMP in vivo by injecting this agent into the L5 dorsal root ganglion (DRG). The central branches of axons arising from these neurons enter the spinal cord and ascend to the brain stem in the dorsal columns of the spinal cord. Seven days after db cAMP injection, the dorsal columns were cut in the thoracic spinal cord. Regenerating sensory axons were visualized in the spinal cord 2 weeks after injury using cholera toxin fragment B conjugated to horseradish peroxidase (CTB-HRP), an anterograde tracer taken up by sensory neurons and transported intra-axonally to the tips of regenerating axons.

Results: Exposing neurons to db cAMP enabled the central branches of sensory axons to regenerate in the dorsal columns of the spinal cord. No regeneration was observed from saline-injected control DRG.

Conclusions: Db cAMP enabled mature sensory neurons to regenerate axons in the dorsal columns of the spinal cord. This finding provided the rationale for examining the ability of this agent to promote the regeneration of retinal ganglion cell axons in the optic nerve.

Retinal Toxicity Secondary to Irofulven

First Author: Michael Lee, MD, Boston, Massachusetts

Background: MGI 114 (Irofulven) is a novel antitumor agent derived from the mushroom product, illudin-S. Although the precise mechanism of action is unknown, irofulven undergoes rapid uptake in sensitive cells, binds to protein and DNA, produces single-strand DNA breaks, and causes cell cycle arrest in "S" phase resulting in cell death. It has been studied in numerous solid tumor Phase II and is currently in a Phase III clinical trial. Transient visual disturbances (modification of color vision and contrast with normal acuity) were reported at the American Society of Clinical Oncology Annual Meeting, May 2001.

Objectives: To describe ERG and visual function testing in 4 symptomatic and 4 asymptomatic patients on MGI 114.

Methods: Irofulven is currently being studied in a multi-center clinical trial of women with metastatic ovarian cancer, who failed previous chemotherapy. A subset of 8 patients from one center underwent comprehensive neuro-ophtalmic evaluation and ERG testing.

Results: Four patients had symptoms including photophobia (100%), reduced vision in bright light (100%), and positive visual phenomena (75%). Visual acuity was mildly affected. Paracentral scotomas and reduction of predominantly cone ERG responses were found in all symptomatic patients. Color plate testing was subnormal in 2 of 4. Para-neoplastic antibodies were tested in 2 of 4 and were negative. Improvement in symptoms, visual function testing, and ERG responses occurred with lower doses or cessation.
Does Topical Brimonidine Tartrate Help NAION?

First Author: Hilary Fazzone, MD, New York, New York

Background: Topical brimonidine tartrate has been reported to have a neuroprotective benefit for retinal ganglion cells following experimental elevation of intraocular pressure and optic nerve injury in the rat. These results were the basis of the recently aborted clinical trial of brimonidine purite for acute non-arteritic anterior ischemic optic neuropathy in humans.

Objectives: We hypothesized that topical brimonidine tartrate would provide neuroprotection for patients with acute NAION.

Methods: We performed a retrospective review of patients with NAION who were evaluated within three weeks of the onset of visual loss and had follow up for at least 8 weeks. 14 of these patients (treated) received brimonidine within 14 days (mean 5.5) of the onset of visual loss. 5 patients were treated after one day of symptoms. The drops were taken QID in 11, TID in 1, and BID in 2 patients. There were 17 control patients (untreated) who were matched to the treated group for age, gender, cardiovascular risk factors, prior aspirin use, and prior first eye NAION. The affected eye visual acuity was expressed as a decimal equivalent. The visual field defects were graded using a previously published scale (0 normal-4 light perception).

Results: The mean baseline acuity (0.56, sd 0.30) and visual field (1.9, sd 0.73) for the treated group was similar to the acuity (0.40, 0.41; p = 0.22) and field (1.9, sd 0.75; p = 0.96) for controls. At the 8 to 12 week examination, the mean visual acuity was 0.29 (sd 0.30) for treated and 0.49 (sd 0.39; p = 0.12) for untreated patients. The mean visual field grade was 2.2 (sd 0.31) for treated and 1.62 (sd 0.70, p = 0.04) for untreated patients. There was no correlation with a worse outcome and delay in initiating therapy and the average time to start the drops was 3.5 days in those who worsened.

Conclusions: Topical brimonidine tartrate, given for NAION after one day, does not appear to offer neuroprotection for this disorder.

Localization of the Pain with Optic Neuritis

First Author: Mark Kupersmith, New York, New York

Background: The pain with eye movement (EOM) in optic neuritis is thought to be due to the movement of the affected intraorbital optic nerve, but this has not been verified. The lack of pain on eye movement in this disorder has also not been explained.

Objectives: To demonstrate whether the MRI localization of the lesion can be related to the pain associated with optic neuritis or the pattern of visual field loss.

Methods: The presence of eye or V1 distribution pain and pain with EOM ipsilateral to the acutely affected optic nerve was recorded in 96 patients (73 women, 23 men, mean age 36 years). The location and length of abnormal optic nerve enhancement on MRI were documented. The presenting visual field defects were characterized as diffuse, central, arcuate, nasal or temporal. As recorded in the ONTT, the visual field sensitivity loss was graded according to the mean deviation (minimal if > -3dB and < -6dB, moderate if > -6dB and < -20dB, severe if > -20dB).

Results: 71 patients experienced eye pain and 67 patients had pain with EOM. 20 patients had no pain. Enhancement of the orbital optic nerve occurred in 68 patients; 91% who had V1 pain (OR 2.54; 95% CI 1.65-4.88) and 88% who had pain with EOM (OR 3.53; 95% CI 1.85-6.74). Enhancement of the canicular, intracranial or both segments was seen, without orbital involvement, in 23 nerves, and 5 nerves had no enhancement. In these 28 patients, 32% had V1 pain (OR .35, 95% CI .21-.61) and 25% had pain with EOM (OR .28, 95% CI .15-.54). In the patients with enhancement limited to the canicular (8) and intracranial (8) optic nerve, 2 and 1 had pain with EOM, respectively. Orbital optic nerve enhancement alone produced central (25%), diffuse (33%), arcuate (28%), nasal (3%) and temporal (0%) field defects. Canicular nerve enhancement alone produced central (50%), diffuse (12%), arcuate (25%), nasal (0%) and temporal (0%) field defects. Intracranial optic nerve enhancement alone produced central (25%), diffuse (12%), arcuate (25%), nasal (0%) and temporal (25%) visual field defects. Nerves with longer segments of enhancement had more eyes with severe field loss (55% vs 32%, p = 0.008).

Conclusions: The majority of patients with optic neuritis with eye or V1 distribution pain or pain with EOM have involvement of the orbital segment of the optic nerve. The absence of pain, particularly with EOM, suggests the disorder is limited to the canicular or intracranial portions of the optic nerve. Except for temporal field loss in eyes with...
intracranial nerve lesions, no pattern of field loss appears related to the location or length of abnormal enhancement.

**Dibutyryl Cyclic AMP Promotes Optic Nerve Regeneration**

**First Author:** Nicholas Monsul, MD, Pittsburgh, Pennsylvania

**Background:** Injured axons do not regenerate in the adult central nervous system (CNS). This reflects the low intrinsic growth state of mature CNS neurons. Presumably, the CNS environment prevents the intrinsic growth state of mature neurons from increasing after injury, thus severely limiting axon regeneration. Intracellular cAMP levels appear to regulate the intrinsic growth state. Exposure to dB cAMP in vivo increases the intrinsic growth state of mature neurons thereby promoting regeneration in the presence of CNS molecules that are potential inhibitors of axonal elongation.

**Objectives:** To determine if an intraocular injection of dibutyryl cyclic AMP (dB cAMP) 24 hours before or 24 hours after axotomy can promote axon regeneration in rat optic nerve.

**Methods:** Intraocular injections of dB cAMP were given 24 hours before (Group A) and 24 hours after (Group B) optic nerve axotomy with a 9-0 nylon. The animals were allowed to survive for 2, 4, 6 and 8 weeks. One day before sacrifice, nerve axotomy with a 9-0 nylon. The animals were allowed to survive for 2, 4, 6 and 8 weeks. One day before sacrifice, 24 hours after optic nerve axotomy results in axon regeneration in rat optic nerve.

**Results:** Intraocular injections of dB cAMP 24 hours before or 24 hours after optic nerve axotomy in vivo increases the intrinsic growth state of mature neurons thereby promoting regeneration in the presence of CNS molecules that are potential inhibitors of axonal elongation.

**Conclusions:** Intraocular injections in vivo of dB cAMP before or after axotomy promote axon regeneration in the optic nerve.

**Eight Index Cases from Field Investigation in Brazil of a Giant Pedigree Of Leber’s Hereditary Optic Neuropathy**

**First Author:** Peter Quiros, MD, Los Angeles, California

**Background:** A mother from rural Brazil had a 14-year-old son go blind in one eye. Her brothers had also gone blind as young adults. Molecular analysis of blood samples showed that all 4 individuals had LHON, 11778, homoplasmic, J-haplotype. Four first-degree relatives from this family living in Massachusetts are also shown to have the same mutation.

**Objectives:** To present preliminary data based on eight index cases from members of a previously unstudied pedigree known to have Leber’s hereditary optic neuropathy (LHON). Epidemiological, neuro-ophthalmological, psychophysical and blood examinations are summarized and subjected to multi-variant analysis on epigenetic factors and gene linkage analysis.

**Methods:** Investigators from the University of Sao Paulo conducted thorough examinations of the 14 year old proband and three of his affected relatives. An extensive questionnaire, previously used on a large LHON pedigree, was further adapted for local conditions and translated into Portuguese. These examinations consisted of the following parts: 1) Epidemiological interview. 2) Blood drawing for molecular analysis, biochemical studies, and gene linkage analysis. 3) Comprehensive neuro-ophthalmological examination. 4) Psychophysical studies including contrast sensitivity, color vision, and threshold Amper grid testing. 5) Humphrey visual field 30-2 perimetry. 6) Fundus photography. Furthermore, the 4 family members living in Massachusetts were similarly examined by US investigators.

**Results:** A total of 8 index cases are presented from this large pedigree. 4 patients were examined in Brazil and 4 others in the U.S. Epidemiological interviews revealed 7 of 8 patients to be heavy smokers and/or drinkers. Nutrition met minimum daily requirements as established by the FDA. Molecular analysis reveals 11778, homoplasmic, J-haplotype in all patients. Biochemical studies are normal. Neuro-ophthalmic and psychophysical testing revealed severe impairments, mean Va CF 3 ft, profound color vision loss, diffuse optic atrophy. Age at onset ranged from 12–23. Involvement of the second eye ranged from 1 week to 18 weeks.

**Conclusions:** 8 cases are presented providing preliminary data from a large pedigree in which 277 members were comprehensively studied. Analysis of environmental risk factors reveal that exposure to toxins such as cyanide from cigarette smoke or folate depletion from ETOH consumption may play a major role in expression of this disease. These preliminary cases provide insight into the largest group of LHON patients ever studied and will help to elucidate genetic and epigenetic factors of this disease.

**The Eyes of Mitomice**

**First Author:** Valerie Biousse, Atlanta, Georgia
Background: The recent creation of several mouse models of mt diseases has provided new insights into the understanding of human mt disorders. Whether these animals have clinical or histologic ophthalmologic abnormalities is of great interest given the high frequency of such abnormalities in humans with mt disorders.

Objective: To describe the currently available mouse models for mitochondrial (mt) diseases and to investigate their ocular manifestations.

Methods: We are currently evaluating the lenses, retinas, optic nerves and extraocular muscles of 3 mouse models for mt diseases. Slit lamp biomicroscopy, electrophysiology (ERG and VEP) and histology (light microscopy and EM) are performed on the mouse models and on age-matched controls.

Results: 1) MnSOD-deficient mice (SOD2tm1Cje) represent a model of increased mt production of reactive oxygen species (ROS). SOD2 mice die early in life from dilated cardiomyopathy. When treated with MnTBAP, mice survive to day 16–20 and have severe neurologic disease. ERGs obtained on SOD2 treated mice at age 19 days demonstrated normal retinal function, however histopathologic studies of the retina showed retinal thinning. Abnormal mitochondria were found in the RPE and in the extraocular muscles. 2) ANT1-deficient mice are models for chronic ATP deficiency. Mice develop classic mitochondrial myopathy and dilated cardiomyopathy. Similar to age-matched controls, ANT mice older than 12 months have nuclear and posterior cataracts. ERG resting revealed supranormal responses in ANT1 mutant mice, which became larger with age. 3) The CAPR chimeric mice have growth retardation and mt myopathy and cardiomyopathy. These mice have a variety of ocular abnormalities including congenital cataracts, decreased ERG amplitudes, and hamartomas of the optic nerves.

Conclusions: These mouse models demonstrate multiple and varied ophthalmologic manifestations. Further (clinical, electrophysiologic) and histopathologic studies are ongoing to better delineate their neuro-ophthalmologic phenotype. An appropriate mouse model for Leber’s hereditary optic neuropathy is also currently under development. Such mouse models should facilitate the understanding of the pathogenesis of human mt disorders and could provide a way of screening therapeutic agents potentially efficacious in human mt diseases.

A Paraneoplastic Syndrome of Combined Optic Neuritis and Retinitis Defined Serologically by CRMP-5-IgG

First Author: Shelley Cross, MD, Rochester, Minnesota

Background: Autoimmune serology has identified two paraneoplastic visual disorders related to small-cell lung carcinoma: retinopathy with 23 kDa recoverin (“CAR”)-IgG, and optic neuritis/vitritis with 62 kDa CRMP-5-IgG.

Objective: To define a novel paraneoplastic ophthalmic disorder and describe neurologic accompaniments.

Methods: CRMP-5-IgG was identified in 172 patients presenting with subacute neurologic disorders. Fifteen patients had optic neuritis, with retinitis documented in 5. Histories and results of ophthalmologic and neurologic examinations, fundus photographs, fluorescein angiograms, and ERGs were reviewed. Bovine retina and optic nerve antigens were analyzed using monoclonal IgGs specific for C-terminal and N-terminal residues of CRMP-5.

Results: All 15 patients (ages 52–74) were smokers; 8 were female. Fourteen had subacute visual loss with swollen optic discs and field defects. Vascular leakage was evident at and remote from the disc; 4/4 tested had abnormal ERGs. Vitreal cells were striking in 9. Two patients with myelopathy and optic neuritis bore a superficial resemblance to Devic’s; one lacked visual complaints, but VER revealed prolonged optic nerve conduction. Other neurologic accompaniments included mental status changes, cranial neuropathies, movement disorders, myelopathy, peripheral nerve disorders, cerebellar and autonomic dysfunction. Small-cell lung carcinoma was confirmed in 10 patients (9 confined to chest); the remaining 5 had another carcinoma or provisional evidence for lung cancer.

CRMP-5-IgG was detected at 1:1,000 to 1:500,000 dilution. No serum had CAR-IgG. CSF in 10/15 was pleocytotic (7–32 cells) with elevated protein and CRMP-5-IgG. Vitrectomy revealed reactive lymphocytosis (4/4), predominantly CD4+ (1/1).

Western blots demonstrated full-length CRMP-5 protein in optic nerve and retina. Peroxidase staining revealed cytoplasmic immunoreactivity in retinal ganglion cells, nerve fiber layer and photoreceptor cells.

Conclusions: CRMP-5-IgG defines a novel paraneoplastic ophthalmologic entity of combined optic neuritis and retinitis accompanied by vitreal inflammation. Its serological confirmation obviates need for vitreous biopsy and mandates a search for small-cell carcinoma.

Pituitary Apoplexy Revisited

First Author: Klara Landau, MD, Zurich, Switzerland

Background: Patients with pituitary apoplexy typically present with severe headache followed by visual loss and
tumor size and male sex were confirmed as risk factors for hypertension. Neuro-ophthalmological signs occurred more frequently in men who may harbor a pituitary adenoma. 

Methods: We reviewed the charts of 378 patients seen at the Division of Endocrinology and Diabetes, University Hospital of Zurich, between 1958 and 2000 with the diagnosis of a pituitary adenoma. Patients with pituitary apoplexy were identified and compared with the rest. In addition, for each patient with pituitary apoplexy two control patients of same age, gender, tumor size, and tumor type were matched for more detailed analysis.

Results: The incidence of classic pituitary apoplexy was 8.5% (n = 32). Sufficient data were available on 26 patients, all of whom had macroadenomas, of which most were nonsecreting. In contrast, only 62% of patients in the comparison group had macroadenomas. Despite a clear female predominance in the whole population, men presented with pituitary apoplexy twice as frequently than women. Comparison of the 26 pituitary apoplexy patients with the 52 matched control patients revealed the following predisposing factors for the development of pituitary apoplexy: estrogen treatment, anticoagulation, diabetes mellitus and hypertension. Neuro-ophthalmological signs occurred more frequently in the apoplexy group whereas endocrine dysfunction was predominant in the control group.

Conclusions: In our large retrospective series both greater tumor size and male sex were confirmed as risk factors for the development of pituitary apoplexy. Early diagnosis of endocrine dysfunction in men who may harbor a pituitary adenoma could efficiently prevent the life-threatening syndrome of pituitary apoplexy.

Relative Sparing of Afferent Pupillary Pathways in LHON: A Postmortem Study

First Author: Swaraj Bose, MD, Irvine, California

Objective: To demonstrate if afferent pupillary fibers are spared in Leber's Hereditary Optic Neuropathy (LHON). It has been previously suggested that pupil light reaction does not exist, because the receptive fields of the parafoveal ganglion cells project directly into the center of the fovea. This explains the clinical finding of macular splitting.

References:
**Results:** Dil labeled fibers were visible on all sections from the superior colliculus to the pretectum in the LHON and control brain along with nuclei in the cell bodies stained with PI. There was a massive loss of small diameter fibers in the LHON optic nerve.

**Conclusions:** The fact that there is considerable staining of the pupillary fibers in LHON lends support to the clinical observation of relatively preserved pupil function in LHON.

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**Retrolaminar Optic Nerve Enhancement on Orbital MRI in Leber’s Hereditary Optic Neuropathy: Clinical and Pathophysiologic Implications**

**First Author:** Michael Vaphiades, DO, Little Rock, Arkansas

**Background:** LHON is a maternally inherited optic neuropathy associated with point mutations in the mitochondrial DNA. It is now recognized that retrolubar optic nerve enhancement with gadolinium administration may occasionally occur in the acute phase of LHON (1).

**Objective:** To determine whether Leber’s hereditary optic neuropathy (LHON) is associated with acute injury to the retrolaminar optic nerve.

**Methods:** Orbital fat suppressed gadolinium enhanced magnetic resonance imaging (MRI) scans on 5 consecutive patients with LHON were evaluated retrospectively from 1996 to present.

**Results:** Optic nerve enhancement was noted in 2 of 5 patients overall, and 2 of 3 patients who were imaged during the acute phase of visual loss. The enhancement persisted for at least 6 months in one patient and resolved after 4 years in the other patient.

**Conclusions:** LHON may be associated with protracted enhancement of the retrolaminar optic nerve. This enhancement may reflect a protracted metabolic disturbance of the optic nerve consequent to mitochondrial dysfunction.

**References:**

Optic Neuritis with Extensive Distension of the Optic Nerve Sheath

First Author: H. E. Killer, MD, Basel, Switzerland

Background: Cerebrospinal fluid is postulated to communicate freely between all interconnected cerebrospinal fluid compartments. The subarachnoid space of the optic nerve resembles a cul-de-sac anatomy and is part of the cerebrospinal fluid system.

Objective: To report a case of unilateral optic neuritis with extensive distension of the optic nerve sheath due to fluid accumulation in the subarachnoid space.

Methods: Interventional case report.

Results: A 38-year-old male patient was admitted because of visual loss in the OD and pain on eye movements. On examination the best visual acuity in the OD measured 20/50 and 20/20 in the OS. 16 out of 18 Ishihara plates were identified with the OD. The papilla in the OD was prominent while the fundus examination of the OS was normal. All laboratory examinations were normal. An MRI of the brain showed no signs of demyelination but massive distension to the right optic nerve sheath with pooling of fluid in the subarachnoid space. The diagnosis of optic neuritis was made and the patient was treated with methylprednisolone. Visual functions in the OD improved over two weeks. An MRI of the orbit was repeated two month later that demonstrated normal diameters of both optic nerve sheaths.

Conclusions: Optic neuritis can lead to an increase of fluid in the subarachnoid space with a consecutive rise of the local pressure. If there is a lack of communication between the subarachnoid space of the involved optic nerve and the chiasmal cistern, an optic nerve sheath compartment syndrome may result.

Retinal Vasospasm During an Attack of Migraine

First Author: H. E. Killer, MD, Basel, Switzerland

Background: Vasospasm plays a major role in the pathogenesis of a number of diseases. Vasospasm can involve blood vessels of different organs, especially the coronaries and the finger arteries. In the brain short spasms occur mostly in the context of migraine. The blood circulation of the eye is often involved the so-called primary vasospastic syndrome and in migraine. The choroid and the vessels of the optic nerve head seem to be affected more often than the retinal vessels.

Methods: Case report of a patient that suffered from a unilateral visual field defect in the OS during a episode of migraine. Fundus examination of the OS demonstrated disruption of blood flow in the lower temporal artery due to vasospasm.

Conclusions: Homonymous scotomas due to occipital hypoperfusion are more common than unilateral scotomas due to retinal migraine. Retinal migraine, however, is of special interest, as the postulated hypoperfusion and the vasospastic constriction can directly be observed on fundus examination.

The Architecture of the Arachnoid Trabeculae and Septae in the Subarachnoid Space of the Human Optic Nerve: Anatomy and Clinical Considerations

First Author: H. E. Killer, MD, Basel, Switzerland

Objectives: To describe the anatomy and the arrangement of the arachnoid trabeculae and septae in the subarachnoid space (SAS) of the human optic nerve and to consider their possible clinical significance for cerebrospinal fluid dynamics and cerebrospinal fluid pressure in the SAS of the optic nerve.

Methods: Postmortem study carried out in 11 subjects without ocular disease. All optic nerves used in this study were obtained no later than 7 hours after death. The study was performed with light microscopy, transmission electron microscopy, and scanning electron microscopy.

Results: The subarachnoid space of the human optic nerve contains a variety of trabeculae and septae. There is a great variability concerning density and anatomic structure depending on the location within the different portions of optic nerve. In the bulbar segment (ampulla) adjacent to the ocular globe, a dens and ramiﬁed meshwork of delicate trabeculae is arranged in a net like fashion. In the midorbital portion, the subarachnoid space is subdivided and at some locations appears even loosely chambered by broad trabeculae and velum like septae. A similar type of trabeculae as observed in the bulbar segment can be found in the intercanalicular portion of the subarachnoid space.

Conclusions: The subarachnoid space of the human optic nerve contains a complex system of arachnoid trabeculae and arachnoid septae that divide the subarachnoid space into a multichambered cerebrospinal fluid compartment.
Due to the architecture of the trabeculae and septae cerebrospinal fluid dynamics are influenced by their presence. The trabeculae and septae described in this study are of delicate character such and can not be visualized even with high resolution magnetic resonance imaging (MRI). The results of this post mortem study may contribute to the understanding of the pathophysiology of asymmetric papilledema, unilateral papilledema and probably normal tension glaucoma.

**Treatment of Acute Visual Loss in Idiopathic Intracranial Hypertension**

**First Author:** Mitchell Strominger, MD, Brooklyn, New York

**Background:** Idiopathic Intracranial Hypertension (IIH) is a condition of unknown etiology leading to elevated cerebrospinal fluid pressure with papilledema in the absence of hydrocephalus. If the disc swelling is severe, patients can present with significant reduction in visual acuity. The treatment of patients with acute visual loss includes oral carbonic anhydrase inhibitors, repeated lumbar puncture, lumbar peritoneal shunts, oral or intravenous corticosteroids, optic nerve sheath fenestration or a combination thereof. In 1994 Liu, Glaser, and Schatz recommended a regimen of methylprednisolone (250mg IV QID x 5 days) in combination with acetazolamide (500 mg BID x 5 days) and ranitidine (150 mg BID x 5 days), followed by prednisone (80 mg per day) tapered over six weeks for the treatment of acute, severe visual loss.

**Objective:** This study was to determine whether the members of NANOS followed the above recommendations.

**Methods:** We surveyed 242 members of NANOS and asked whether they followed the recommended treatment regimen. We defined severe, acute visual loss as visual acuity worse than 20/30 or visual field defect of grade 3 or worse. If not, we asked them to specify their preferred treatment.

**Results:** 44 (18%) returned the survey by fax. 30 ophthalmologists, 6 neurologists, 5 with training in both, and 3 did not indicate. 11 (25%) used the recommended treatment regimen. Of the remaining 33 (75%) respondents, many modifications were noted. 10 used higher doses of acetazolamide including 3 who recommended intravenous. Two tapered the prednisone more rapidly. 18 (55%) included optic nerve sheath fenestration or lumbar peritoneal shunting.

**Conclusions:** There is no consensus as to the treatment of acute visual loss in IIH. Most physicians used some modification of the recommended regimen with the addition of ONSF or LP Shunting. Further studies are needed to determine the best treatment of this disorder.

The Evaluation of Isolated Third Nerve Palsy Revisited: an Update on the Evolving Role of Magnetic Resonance, Computed Tomography, and Catheter Angiography

**First Author:** Andrew Lee, MD, Iowa City, Iowa

**Abstract:** The evaluation and management of the neurologically isolated third nerve palsy continues to evolve. The major concern for the clinician confronted with a patient with a third nerve palsy has been the exclusion of an intracranial neurism. The evolution of new imaging techniques such as computed tomography angiography (CTA) and magnetic resonance angiography (MRA) have provided new imaging options for clinicians. This paper reviews the pertinent recent literature on the use of these imaging studies in evaluating the patient with a third nerve palsy.

Posterior Ischemic Optic Neuropathy Complicating Laparoscopic Prostatectomy

**First Author:** Clifton Otto, MD, Tacoma, Washington

**Background:** Posterior ischemic optic neuropathy (PION) is a rare condition that typically occurs intra-operatively from sustained hypotension, anemia, or direct pressure to the globe, resulting in ischemic infarction of the retrobulbar portion of the optic nerve. PION can also be caused by elevated episcleral-venous pressure, as demonstrated by this first case following laparoscopic prostatectomy.

**Objective:** To present a case of posterior ischemic optic neuropathy (PION) secondary to laparoscopic prostatectomy.

**Methods:** Case report with discussion of findings.

**Results:** This 65-year-old male presented with acute onset of loss of vision in the temporal field of the OD after regaining consciousness following a fifteen-hour laparoscopic prostatectomy. The patient received 15 L of crystalloid during this procedure to maintain urine output. Marked swelling of the patient’s eyelids, face and upper extremities was noted by anesthesia halfway through the procedure, but there was no prolonged hypotension, significant anemia, or evidence of direct pressure over the eyes reported during surgery. Formal visual fields revealed a temporal scotoma in the OD consistent with the patient’s subjective loss of vision, a finding that was not present on previous visual fields obtained for management of glaucoma in the other eye. No optic nerve swelling or retinal hemorrhage was present. Visual fields obtained over the following eight months showed mild progressive improvement in the temporal field of the OD, corresponding with the patient’s subjective observation of gradual expansion of his temporal...
field of vision. Carotid artery duplex and MRI of the brain and orbits were both normal.

Conclusions: Given the lack of intraoperative hypotension, anemia or direct pressure to the globe in this case, sustained elevation of episcleral venous pressure during surgery is the most plausible cause of this patient's optic neuropathy. Intraoperative findings suggest that measures should be taken to prevent excessive periorbital swelling during prolonged surgery.

The Obvious Is Not So Obvious

First Author: Adam Cohen, MD, Burlington, Vermont

Objectives: To describe an unusual presentation of giant cell arteritis; to discuss a plethora of teaching points, and review the medical literature on orbitopathy secondary to giant cell arteritis.

Methods: Case Report.

Results: A 67-year-old man presented 12/99 with decreased vision in both eyes, particularly over the prior month. His medical history included biopsy-proven giant cell arteritis (diagnosed 9/99), Type 2 diabetes mellitus, atrial fibrillation necessitating amiodarone (started late 11/99), and alcoholism. Due to concern about the impact of systemic corticosteroids on his diabetes, and avoidance of methotrexate given his long history of alcoholism and probable liver damage, he was started on pulse cyclophosphamide therapy to facilitate the corticosteroid taper. He was admitted to the hospital 12/99 with a 2-week history of progressive right upper and lower extremity edema, generalized weakness, and bilateral visual loss. bedside neuro-ophthalmologic examination revealed visual acuities of 20/200 OU with bilateral proptosis and “tight orbits”, lid edema, conjunctival chemosis, mildly elevated optic discs with sectoral right optic disc pallor, and moderate background diabetic retinopathy with minimal macular involvement in both eyes. Computed tomography was remarkable for bilateral proptosis, with normal extraocular muscles, orbital fat, and paramosal sinuses. His Westergren erythrocyte sedimentation rate was 67; having been 22 one-week prior, and C-reactive protein was 4.7. Thyroid function tests were normal. Concurrent with discontinuation of the amiodarone, intravenous methylprednisolone one gram daily was initiated. After further visual decline, bilateral transconjunctival orbital decompression surgery was performed, with bilateral orbital fat biopsies, stains, and cultures, which were unremarkable. Despite decreased proptosis and “softer orbits”, vision failed to recover in either eye.

Conclusions: Giant cell arteritis may present in a variety of ways, including bilateral orbital ischemia resembling inflammatory orbital pseudotumor or dysthyroid orbitopathy.

Ocular Bartonellosis Mimicking Ocular Metastases

First Author: Aki Kawasaki, MD, Lausanne, Switzerland

Background: Bartonella henselae is the causative agent of cat-scratch disease. In 5–10% of cases, the eye is involved. Two well-known, ocular complications are conjunctivitis and neuroretinitis. Other posterior segment manifestations are increasingly recognized including inflammatory choroidal lesions (white spots), serous retinal detachment, vaso-occlusive disease and optic disc granulomas.

Objective: To report a patient who had multiple mass lesions in one eye (optic disc, macula, peripheral retina) and positive serologies for acute Bartonella henselae infection.

Methods: Case report.

Results: A 12-year-old boy developed headache and visual loss in his OS to 20/400 acuity. Funduscopy showed marked optic disc swelling with peripapillary subretinal elevation. A large creamy-colored mass was present in the macula as well as smaller, discoid-shaped elevated lesions in the periphery. An inferior serous retinal detachment was also present. There was no evidence of ocular inflammation. Ultrasound confirmed the presence of a solid mass at the optic disc and at the macula. Workup for possible metastatic disease was negative. Bartonella serologies were initially negative then showed greater than fourfold rise in titers one month later. The patient was treated with doxycycline, the ocular masses disappeared within 4 weeks and vision recovered to 20/70.

Conclusions: We report the first case of a macular mass presumably due to Bartonella infection. The presence of multiple mass-like lesions in the absence of systemic or ocular inflammation was suggestive of ocular metastases. We alert the clinician to yet another clinical presentation of cat-scratch disease.

Orbital Infarction after Intranasal Cocaine

First Author: Gregory Van Stavern, MD, Detroit, Michigan

Background: Orbital infarction syndrome is uncommon, and results from ischemia of all intraocular and orbital structures. It has been reported in a variety of settings. Cocaine has potent sympathomimetic and vasactive properties, and has been associated with retinal vascular occlusions. We describe a case of orbital infarction syndrome associated with intranasal cocaine use.
Objective: To describe an uncommon syndrome, as well as a previously unreported complication of intranasal cocaine use.

Results: A 36-year-old woman presented with sudden, painful visual loss OS, and complete left ophthalmoplegia. The patient had attended a party the previous evening, and consumed alcohol, and intranasal cocaine. She lost consciousness with her left face pressed against a desktop. She awoke with complete blindness in the OS, left orbital pain, left ptosis, left proptosis, and complete left ophthalmoplegia. An urgent MRI, including fat-suppressed orbital views, showed diffuse edema of all left extraocular muscles, but no other abnormalities. MRA/MRV were normal. A cerebral angiogram, performed 48 hours after the patient had awoken, was normal, with questionable delayed choroidal filling. Bedside examination showed VA of 20/20 OD, NLP OS. She had complete left ptosis, mild periorbital edema, and complete left ophthalmoplegia. The left fundus showed diffuse retinal edema. The remainder of her neuro-ophthalmic examination was unremarkable. An extensive inflammatory and hypercoagulable evaluation was unrevealing. She was seen one week later in clinic. The orbital pain was improved. Examination was similar, except for modest improvement in left ductions and left ptosis. The retinal edema had resolved.

Conclusions: Orbital infarction has been described in patients with prolonged head compression, as well as a variety of inflammatory and hypercoagulable disorders. The combination of left orbital compression and the vasoactive properties of cocaine resulted in orbital infarction syndrome in this patient. This potential complication of intranasal cocaine has not previously been reported.

Unusual Visual Loss in Papilledema Associated with Parapapillary Neovascular Membrane

First Author: François Borronut, MD, Lausanne, Switzerland

Background: The incidence of visual loss amongst patients with idiopathic intracranial hypertension (IIH) ranges from 10% to 26%. Causes of visual loss include optic atrophy, anterior ischemic optic neuropathy, arterial or venous retinal occlusion, maculopathy, and subretinal neovascular membrane (NVM).

Objective: To report an unusual case of visual loss secondary to NVM in a patient with otherwise asymptomatic IIH.

Methods: Case report.

Results: A previously healthy 39-year-old man presented with left visual loss for 2 weeks. Visual acuity was 20/20 RE and 20/30 LE. Visual field revealed enlarged blind spot and cecocentral scotoma in the OS. Vitreous cells were present in the OS with a slight inflammation in the left anterior chamber. Fundus examination revealed bilateral swollen optic discs with bilateral temporal superior parapapillary subretinal nodules (1.9 and 2.3 mm on B-scan echography) and left partial macular star. Results of lumbar puncture and blood serologies for inflammatory and infectious disorders were twice negative. Vision progressively worsened to 20/100 due to the progression of the left macular star. Bilateral parapapillary NVM were suspected. Intraventricular intracranial pressure was continuously monitored revealing nocturnal sustained peaks of hypertension (max. 40 cmH2O during 15–20 minutes, 10–12x/night). Lumbo-peritoneal shunt was performed. Evolution was then favorable with improvement of left visual acuity to 20/30 and spontaneous involution of NVMs.

Conclusions: Parapapillary NVM is a rare event complicating papilledema, as only 10 cases have been thus far reported in the literature. It is believed to be associated with long-standing papilledema. Indeed half of the reported cases (including the present case) are asymptomatic until visual loss. Successful treatment of IIH is frequently followed by spontaneous involution of the NVM. However, 4/7 cases failed to recover visual acuity. Early recognition and treatment of IIH might improve visual prognosis of patients with associated NVM.

Neuro-Ophthalmic Manifestations of Patients with Unruptured Intracranial Aneurysms

First Author: M. Tariq Bhatti, MD, Gainesville, Florida

Objective: To determine the frequency of neuro-ophthalmic findings in patients with unruptured intracranial aneurysms and to correlate patient characteristics and outcome with these findings.

Methods: A retrospective chart review of 186 consecutive patients with unruptured intracranial aneurysms operated at the University of Florida by a single surgeon (ALD) between 1989 and 1994. Analysis was performed on the clinical characteristics of patients with only preoperative or postoperative ophthalmic findings. Preoperative presenting ophthalmic findings were analyzed to determine their resolution, improvement, stability, or worsening at final follow-up. Ophthalmic outcomes were correlated with patient age, duration of symptoms prior to surgery as well as size of the aneurysm(s).

Results: Sixty-three (34%) of 186 patients with unruptured intracranial aneurysms had ophthalmic signs or symptoms. Fifty-six (89%) were females and 7 (11%) were males. Fifty-seven (89%) were Caucasians. Age ranged from 18 to 75 years (mean age 53 years + SD). The most common aneurysm location was the ophthalmic artery (33%) followed
by the posterior communicating artery (23%). In 62% (39/63) of patients, the ophthalmic findings were the presenting manifestation of the aneurysm. The presenting manifestations in descending order of frequency were diplopia (23%), decreased vision (17%), headache (15%), visual field defects (14%) and retro-orbital pain (6.3%). Shorter duration time of symptoms prior to surgery was not associated with an increased incidence of postoperative ophthalmic improvement (< 1 month, 45% versus > 1 month, 60%). There was a statistically significant correlation between younger age and improved outcome of the presenting sign or symptom. Furthermore, improved outcome was more likely to occur in patients with small (1-14 mm) aneurysms. Large (15-24 mm) and giant (>25 mm) aneurysms were associated with an almost equal chance of improved or worsened symptoms. Forty-one percent (26/63) of patients had multiple aneurysms. Postoperatively, forty-one percent (26/63) of patients developed ophthalmic findings that were not present before surgery. Of these new findings, ptosis and anisocoria were more likely to improve when compared with ocular motility disturbances.

Conclusions: Neuro-ophthalmic manifestations are common in patients with unruptured intracranial aneurysms and can often be the presenting feature. The outcome of ophthalmic findings seems to be related to age of patient and size of the aneurysm. Early surgery was not associated with a greater likelihood of improved ophthalmic outcome. A large proportion of patients with ophthalmic findings have multiple aneurysms, some of which may be remote from the visual and ocular motility pathways.

Spatiotemporal Profile of Cortical Responses to Visual Motion Stimuli Analyzed by MEG

First Author: Satoshi Kashii, MD, Kyoto, Japan

Objective: To elucidate the spatiotemporal activity of a cortical network for processing the motion perception, a magnetic encephalographic (MEG) study was performed in six healthy right-handed subjects.

Methods: A random dot kinematogram was used for the visual stimuli. It consists of 120 white square dots randomly projected on a screen against a global dark background. The subjects were instructed to look at the fixation point at the center of the screen with both eyes. Each dot moved smoothly at a constant speed. Coherent movement of 390 milliseconds duration and random movement of 1320 milliseconds were presented alternately. During the coherent period, a certain proportion of the total dots (i.e. 50, 70 and 100%) moved in a uniform direction, whereas the rest of the dots moved in random but constant directions. The magnetic responses were recorded in a magnetically shielded room using a 122-channel whole-head magnetometer.

Results: Two components of magnetic fields were observed in the bilateral temporal and occipital areas in all subjects, with right temporal dominance. We focused on the first component in the right temporal area as they had large amplitudes and were readily distinguished. As the coherence levels rose, the peak latencies of the first component shortened markedly. The mean latencies (± SD) for the coherence level of 100, 70 and 50% were 233 ± 21.6, 250 ± 22.5 and 278 ± 35.4 milliseconds, respectively. Estimated sources of the first components in all subjects were consistently identified in the right lateral occipitotemporal cortex, the human MT/V5. As the coherence level increased from 50, 70 to 100%, the dipole strength increased from 3.8 ± 3.1, 5.0 ± 3.9, to 8.3 ± 6.9 nAm, respectively.

Conclusions: These results suggest that the coherence level of dot motion stimulus is reflected in the net activation of hMT/V5.

The Effect of Optic Disk Edema on Spontaneous Venous Pulsations in the Absence of Elevated Intracranial Pressure

First Author: Timothy McCulley, MD, Cincinnati, Ohio

Background: Although often considered a sign of elevated intracranial pressure, alternative factors may influence the loss of spontaneous venous pulsations of the optic disk.

Objective: To evaluate the effect of optic disk edema on spontaneous venous pulsations in the absence of elevated intracranial pressure.

Methods: Twenty consecutive patients with unilateral optic disk edema due to anterior ischemic optic neuropathy (n = 11) or optic neuritis (n = 9) and a normal contralateral optic nerve were evaluated for the presence of spontaneous pulsations of the superficial veins of the optic nerve head in both eyes. The proportion of subjects with spontaneous venous pulsations present in both eyes, in the involved eye only, in the uninvolved eye only, and in neither eye was determined. Exact McNemar's test was used to evaluate an effect of optic disk edema on the presence of spontaneous venous pulsations.

Results: Spontaneous venous pulsations were observed in 60% (12/20) of uninvolved eyes and 5% (1/20) of eyes with optic disk edema. This difference was statistically significant (p < 0.005). Venous pulsations were absent in both eyes of seven subjects, and present only in the uninvolved eye of twelve patients. No subject had venous pulsations present in both eyes. One patient with ischemic optic neuropathy and
segmental optic disk edema had a venous pulsation present on the non-edematous half of the nerve.

Conclusions: Optic nerve head edema may cause the cessation of spontaneous venous pulsations in the absence of elevated intracranial pressure.

Isolated Neurogenic Blepharoptosis Secondary to Traumatic Eyelid Injury

First Author: Timothy McCulley, MD, Cincinnati, Ohio

Background: Isolated neurogenic blepharoptosis is rare and when encountered usually due to compression of the oculomotor nerve.

Objective: To describe a series of patients with isolated neurogenic ptosis secondary to traumatic eyelid injury.

Methods: Case series.

Results: Three previously healthy patients (2 males, 1 female; ages 29, 37, and 39) were evaluated for blepharoptosis following eyelid trauma. All three injuries involved forceful anterior displacement of the involved upper eyelid by a finger placed under the eyelid. Two occurred during domestic altercations and one while the patient was playing basketball. All patients were evaluated within 48 hours of injury and found to have complete ptosis with no levator function, consistent with loss of innervation to the levator palpebrae superioris muscle. Additional findings included minimal eyelid ecchymosis and edema in all cases and subconjunctival hemorrhage in two cases. All patients had full ocular motility and were orthophoric in all fields of gaze with no anisocoria. The remainder of the examinations of the involved and contralateral eyes was unremarkable with visual acuities correctable to 20/20. All cases were managed conservatively with observation only, and within two weeks all three patients had recovered completely with normal symmetric lid height and levator function.

Conclusions: Ptosis secondary to isolated injury to the oculomotor nerve branch to levator palpebrae superioris may result from traumatic anterior displacement of the upper eyelid. Complete resolution is likely within two weeks.

Surgical Treatment of Skew Deviation

First Author: Robert Sanke, MD, Oklahoma City, Oklahoma

Background: Skew deviation is a supranuclear vertical ocular misalignment, which may cause comitant or non-comitant hypertropia. Alternating hypertropia on lateral gaze is a common pattern, and the incomitance of this condition makes strabismus surgery challenging.

Objective: To evaluate results of strabismus surgery for skew deviation.

Methods: A retrospective chart review of patients with skew deviation seen from January 1992 until November 2001 was undertaken. Ten patients who underwent strabismus surgery for skew deviation were identified. Successful outcome was defined as 2 prism diopters or less of vertical deviation in the primary position, coupled with patient satisfaction on subjective questioning.

Results: The most common cause of skew deviation was stroke, which was seen in 6 patients. Eight of the 10 patients were successfully treated, 6 with one surgical procedure and 2 with two procedures. Patients with alternating hypertropia (bilateral inferior rectus skew pattern) were treated with bilateral inferior rectus resection, and in one case with subsequent bilateral superior rectus recession. Patients with non-alternating or comitant hypertropias were treated with either ipsilateral inferior rectus resection or contralateral inferior rectus recession. One case of skew occurred with a comitant exotropia and was successfully treated with vertical transposition of the horizontal rectus muscles. The two patients who failed surgical management were treated with a combination of oblique weakening procedures coupled with vertical rectus surgery.

Conclusions: Skew deviation can be amenable to strabismus surgery. For alternating hypertropia, bilateral inferior rectus resection is our treatment of choice and may be coupled with superior rectus recession when needed. Non-alternating or comitant vertical deviations are well managed with conventional vertical rectus muscle surgery, but vertical transposition of the horizontal recti may be useful when there is an accompanying large horizontal deviation. Oblique muscle surgery is ineffective and not recommended for this condition.

Should Phenylephrine Be Used as a Topical Mydriatic Agent in Ischemic Optic Neuropathy?

First Author: Misha Pless, MD, Pittsburgh, Pennsylvania

Objective: To report 4 patients with the diagnosis of non-arteritic ischemic optic neuropathy (NA-ION) who experienced acute worsening of visual function after instillation of phenylephrine for dilated funduscopic examination.

Methods: A retrospective chart review of 125 patients treated in the Neuro-ophthalmology unit of the University of Pittsburgh’s Eye and Ear Institute between 1996 and 2001 with the diagnosis of NA-ION.

Results: Between 1996 and 2001, 4 patients (age range 54-82, 1F 3M) were identified who experienced acute worsening of visual function immediately or shortly after
administration of topical mydriatic agents given for fundusscopic visualization and diagnostic purposes. In all cases one drop each of 2.5% phenylephrine and 0.5–1% tropicamide was used. Three patients had classic risk factors such as hypertension, diabetes, and had a contralateral “disc at risk.” The female and youngest patient had ION presumed secondary to Lupus. The range of time from acute visual loss to presentation to neuro-ophthalmic care ranged from 1–6 days. The time of onset of the decline in visual function ranged from 45 minutes (patient with lupus) to 12 hours after instillation of mydriatic drops. Visual acuity at diagnosis ranged from 20/40–20/400.

Conclusions: Phenylephrine is a mydriatic which has vasoconstrictive properties and which may be absorbed by the cornea, thus yielding non-negligible intraocular concentrations. Vasoconstriction of the watershed posterior ciliary capillary beds may occur as a result. This may cause further infarction of already compromised circulatory territories in edematous optic nerves. Because phenylephrine is a known vasoconstrictor in vivo and in vitro it is potentially more likely to cause deleterious vasoconstriction and an acute decline in visual function in patients with acute ION, than tropicamide. After reviewing these data I have modified my practice so phenylephrine is no longer used to dilate pupils of patients with ION or retinal artery occlusion.

Möbius Syndrome Plus

First Author: Jacqueline Leavitt, MD, Rochester, Minnesota

Objective: To report a patient with Möbius-like syndrome with intact lateral rectus function and multisystem abnormalities including: hypogonadism, short stature, peripheral neuropathy, mental retardation, hearing loss, and anosmia.

Methods: Case report and literature review.

Results: 23-year-old woman admitted for GI pain. History of intrauterine growth retardation. She has short stature, hypogonadism, hearing loss, anosmia, mental retardation, and progressive sensorimotor peripheral neuropathy. Family history was negative for ptosis or any EOM problems. Since childhood she has had facial diplegia and ophthalmoparesis. She has incomplete asymmetric ptosis, large angle exotropia, intact lateral gaze but marked deficit of supraduction and adduction OU. Dolls head maneuver was negative. Pupils were 3mm and nonreactive. MRI: Asymmetric skull, colpocephaly, atrophic corpus callosum, small cerebral peduncles and periatrial white matter atrophy. Workup for mitochondrial cytopathy was negative.

Conclusions: Möbius originally described facial diplegia and bilateral abducens palsy. Subsequently cases in the literature have been called Möbius syndrome that have facial diplegia associated with a host of other cranial nerve palsies. This case may represent a separate entity from Möbius syndrome and has more extensive systemic and cranial nerve involvement than previously described cases of Möbius and hypogonadism and neuropathy.

Photophobia in Patients with Pseudotumor Cerebri

First Author: Deborah Friedman, MD, Syracuse, New York

Objective: To determine the prevalence of photophobia at the time of diagnosis of Pseudotumor Cerebri (PTC).

Methods: Neuro-ophthalmic medical records of 180 patients with a diagnosis code of PTC or papilledema from 1991 to 2000 were obtained. Eighty-two patients met predetermined criteria for the diagnosis of PTC. These records were systematically reviewed (DIF) to determine if photophobia was reported by patients at their initial presentation of PTC.

Results: Five patients (6%) indicated photophobia during their first interview, which was often severe.

Conclusions: Our retrospective review indicates that photophobia as one of the presenting symptoms of PTC is uncommon but, when present, can be quite dramatic. Review of the literature indicates that it is rarely reported. It is unclear whether the photophobia in PTC is etiologically related to other central causes of photophobia.

Adjuvant therapy for invasive sino-orbital fungal infection

First Author: Roger Turbin, MD, Newark, New Jersey

Background: The treatment of invasive sino-orbital fungal infection is complicated both by the presence of comorbid medical conditions, and the resulting disfigurement of radical surgical debridement. Both of these factors limit therapeutic options. Aggressive surgical debridement, often including extensive sinus surgery supplemented by exenteration and administration of systemic antifungals, is common. Despite aggressive surgical and medical intervention, however, these infections typically result in a prolonged disease course with high morbidity and mortality.

Objective: To report the authors’ experience in the management of invasive sino-orbital fungal infection treated with retrobulbar injection and surgical or postoperative irrigation of amphotericin B (AmphB) as an adjuvant to systemic antifungal therapy, and limited, conservative, biopsy or debridement procedures.

Methods: Retrospective chart review of a consecutive case series. Data concerning comorbid conditions, vision,
motility and orbital examination, radiographic findings, and clinical outcome are provided. Fungal species, treatment data, and surgical procedures are described.

Results: Five patients suffered biopsy-proven invasive fungal sino-orbital infection (2 rhizopus, 1 mucor, 1 aspergillosis, 1 rhodotorula mucilaginosa/alternaria/hormographiella) related to comorbid conditions (leukemia, renal transplant, diabetic keto-acidosis, corticosteroid therapy, retained intraorbital foreign body). Adjuvant therapy supplementing systemic antifungal therapy included retrobulbar/peribulbar injection (3-5 mL of 2mg/cc Amphotericin B) and sino-orbital irrigation (50–500cc of 0.2–0.5mg/cc Amphotericin B). Two patients who presented prior to the onset of complete blindness (counting fingers, and 20/40 soon worsening to no light perception) in the affected eye maintained useful visual function at latest examination (20/80 and 20/25, respectively). Five patients showed improvement in orbital and motility examination parameters. No patient required orbital exenteration, or extensive disfiguring facial debridement.

Conclusions: Adjuvant orbital therapy with Amphotericin B is safe and appears effective in controlling orbital fungal infection. In selected cases, it may prevent disfiguring surgery, may be associated with improvement in ophthalmoplegia, and may preserve visual function when begun prior to onset of complete blindness.

Retinopathy in Patients with Diabetic Ophthalmoplegia

First Author: Lucas Trigler, MD, Oklahoma City, Oklahoma

Background: Intuition suggests that the incidences of diabetic retinopathy and CN palsy are directly proportional, but this has not been proven.

Objective: To review clinical characteristics, prevalence, and severity of retinopathy in patients with diabetes with cranial nerve (CN) III, IV, and VI palsies, and to determine if type or duration of diabetes, or severity of retinopathy correlates with cranial neuropathies.

Methods: Retrospective chart reviews of patients with CN III, IV, or VI palsy were performed at the Bascom Palmer Eye Institute (BPEI) from 1/91 through 12/97 and at the Dean A. McGee Eye Institute (DMEI) from 1/94 through 7/01. Patients were included if DM was determined to be the etiology of the CN palsy. Prevalence and severity of retinopathy were compared with data from the Wisconsin Eye Study for Diabetic Retinopathy (WESDR) as a control.

Results: Of 2,229 patients with ocular motor CN palsy, 307 (13.8%) were due to DM. The prevalence of CN involvement was: VI (50%), III (43.3%), and IV (6.7%). At each location, the prevalence of retinopathy with respect to duration of diabetes was lower in both IDDM and NIDDM. Type II patients with diabetes as compared with controls (BPEI p = 0.009 and p = 0.005; DMEI p = 0.004 and p = 0.29). When data from both locations was combined, the difference was even more significant (IDDM p = 0.001 and NIDDM p = 0.006). There were no significant differences between the two locations in gender, type or duration of DM, age at presentation, or frequency of CN involvement. All three populations differ with respect to time period studied and racial distribution.

Conclusions: Type II patients with diabetes with ocular motor CN palsy have significantly less diabetic retinopathy than controls. Theories that explain this observation will be presented.

Charles Bonnet Syndrome Precipitated by Brimonidine Tartrate Eye Drops

First Author: Robert Tomsak, MD, Cleveland, Ohio

Background: Brimonidine tartrate (BT) (Alphagan) is an alpha-2 adrenergic agonist marketed for treatment of primary open angle glaucoma (POAG) and may have neuroprotective effects (1). One report of acute delusional psychosis with auditory hallucinations in a 68-year-old man treated for POAG is published (2). Here I report two patients with bilateral vision and visual field loss from monarteritic anterior ischemic optic neuropathy and optic nerve drusen who also had elevated intraocular pressures. Both developed visual hallucinations (Charles Bonnet syndrome; CBS) shortly after beginning the use of BT eye drops (3).

Objective: To report Charles Bonnet syndrome precipitated by the use of brimonidine tartrate eye drops (Alphagan) in two elderly visually compromised women.

Methods: Observational case series of two patients. Clinical office exams and telephone interviews.

Results: Brimonidine tartrate use apparently precipitated the Charles Bonnet syndrome in both cases and cessation of drug did not stop hallucinations.

Conclusions: Both patients described above were candidates for the CBS but neither had visual hallucinations prior to using BT. The hallucinations did not completely stop after BT was discontinued, although confusion rapidly cleared. Visual hallucinations caused by oral clonidine, another alpha-2 adrenergic agonist, are well documented (4,5). Auditory hallucinations, depression, confusion and anxiety have been reported with BT (2) and clonidine (4,5). Brimonidine tartrate use may cause visual
hallucinations when administered to elderly patients with significant bilateral vision and visual field impairment.

References:

An Atypical Bruit

First Author: Mitchell Wolin, MD, Greenville, South Carolina

Abstract: A 46-year-old female started having diplopia about 5 days prior to presentation. This was initially noted when driving and then became more constant. She was aware of diplopia the prior week while in the hospital for a kidney biopsy. The patient had recently been under evaluation for a kidney problem. She had been found to have elevated urinary protein, and underwent kidney biopsy, and she required 2 units of blood the following day. She has had headaches for about 2 months. She had also been fatigued recently. She had been aware of a roaring sound in her head for about 5 weeks that was either constant or pulse like. This worsened with laying down. This roaring sound started about one week following an upper respiratory infection that subsequently resolved. PMII is notable for an old heart murmur. She has had headaches on a recurrent basis in the past measuring 16 ET in right gaze, 18 D in primary and 14 D in left gaze. Discs revealed 1+ edema OU. Auscultation of the head revealed a somewhat high-pitched bruit, best heard in the temples and consistent with the pulse rate. Review of the kidney biopsy showed mild focal global glomerular sclerosing change, suggestive of low-grade focal sclerosing nephropathy. It was debated whether to proceed directly to cerebral arteriography, given the suggestive findings of a dural carotid cavernous fistula. However, a CT scan was obtained which showed an apparent mass in the region of the torcular, with homogenous and intense enhancement with erosion of the inner table of the occipital bone. Angiography did not show any CC fistula, but did show findings of significant flow through the mass and no obliteration of the veins. There is no arterial shunting to the tumor mass. A neurosurgeon felt that this did not represent a meningioma, and possibly representing an eosinophilic granuloma. An MRI scan was performed which showed the torcular mass. It was decided to proceed with an open biopsy of the mass, which was performed on 10-29-99 without complications. This revealed a plasmacytoma. She underwent bone marrow biopsy, which confirmed the impression of multiple myeloma. It was determined that the nephrotic syndrome was due to Bence Jones proteinuria. She subsequently underwent treatment with chemotherapy. She developed severe renal failure after about 5 months, and died about 1 year after diagnosis. An audible cranial bruit in the setting of mild bilateral 6th nerve palsies and mild papilledema initially suggested the possibility of a carotid cavernous fistula. The finding of a mass lesion in the back of the head due to a plasmacytoma from undiagnosed multiple myeloma was quite unusual. The nephrotic syndrome was determined to be secondary to the urinary protein from the myeloma.

Isolated Pupil-Dilated Painful Third Nerve Palsy as an Initial Presentation of Systemic Lymphoma

First Author: Grace Kao, MD, Orange, California

Background: “The rule of the pupil” has implied that pupil-dilated third nerve palsy is usually due to a compressive lesion, and pupil-sparing to an ischemic metabolic or non-compressive, reversible lesion. This notation is challenged in some conditions of pupil-dilated third nerve palsy with systemic lymphoma.

Objective: To report a case of complete third nerve palsy violate “the rule of pupil” and possible mechanism.

Methods: Case report and review of literature.

Results: A 41-year-old healthy white man developed a progressive painful left third nerve palsy over 2 weeks to a complete palsy with a fixed 7.5 mm pupil after a severe flu. He otherwise had normal neurologic and neuro-ophthalmological examination. Brain and orbit MRIs did not show any abnormality except more enhanced left superior ophthalmic vein than the right. Cerebral angiogram, CSF profile, cytology, virus titer, PCR and cultures of herpes viruses, Lyme disease, angiotensin-converting enzyme were all negative. Eye pain resolved after IV methylprednisolone 1 g/d for 3 days but not the ocular palsy until 6 weeks later. Two months after the onset, when left third nerve almost resolved, he had another flu followed by left facial palsy and hoarseness. Repeated MRI of brain was negative. CSF showed 129 WBC, 83% lymphocyte, protein 91 mg/dl and rest of CSF bacteria and viral cultures, titers, PCR, ACE titer was negative as well as flow cytometry. Facial palsy resolved after one day IV methylprednisolone. Further workup revealed plural effusion and mediastinal mass on CT scan. Mediastinoscopic biopsy after steroid for 5 days revealed necrotic fibrotic tissue. He remained stable until 6 weeks later when he had dysphagia and breathing difficulty. The mediastinal mass recurred with pericardial...
effusion. CSF showed 219 WBC with 87% lymphocyte and 11% atypical lymphocyte, protein 160 mg/dl, glucose 66 mg/dl. Flow cytometry of CSF was diagnostic for T-cell lymphoblastic lymphoma. He was then treated with systemic and intrathecal chemotherapy followed by whole brain irradiation with remission until 3 months later when he developed severe multifocal motor sensory peripheral neuropathy. Left third nerve function has remained almost resolved.

Conclusions: Isolated third nerve palsy with fixed dilated pupil without radiologically demonstrated lesion and normal CSF can be a preceding sign of systemic malignant lymphoma. A microinfiltrative process not radiologically visible of the third nerve proximal to the orbital apex is the presumptive mechanism. Only 4 reports in literature described isolated third nerve palsy in lymphoma and none had a complete palsy with a full blown pupil that recovered later despite systemic recurrence.

Adaptive Neural Mechanism for Listing’s Law Revealed in Patients with Fourth Nerve Palsy

First Author: Agnes Wong, MD, St. Louis, Missouri

Background: During fixation and saccades, human eye movements obey Listing’s law, which specifies the eye’s torsional angle as a function of its horizontal and vertical position.

Objective: To investigate whether the brain adapts to defective torsional control after fourth nerve palsy.

Methods: Thirteen patients with fourth nerve palsy (11 chronic, 2 acute), and ten normal subjects were studied using scleral search coils. With head immobile, subjects made saccades to a target that moved between straight ahead and 8 eccentric positions. From the eye position data, we computed a plane of best fit, called Listing’s plane. Violations of Listing’s law were quantified by computing the ‘thickness’ of this plane, defined as the standard deviation of the distances to the plane from the data points.

Results: Patients with chronic fourth nerve palsy obeyed Listing’s law in both the paretic and non-paretic eyes during fixation and saccades; however, Listing’s planes of both eyes had abnormal orientations, being rotated temporally. In contrast, the paretic eye of patients with acute palsy violated Listing’s law during saccades. During downward saccades, transient torsional deviations moved the paretic eye out of Listing’s plane. Torsional drifts returned the eye to Listing’s plane during subsequent fixation.

Conclusions: During saccades, acute fourth nerve palsies violate Listing’s law, whereas chronic palsies obey it, indicating that neural adaptation can restore Listing’s law by adjusting the innervations to the remaining extraocular muscles. Although Listing’s law is obeyed in chronic palsy, Listing’s plane is rotated temporally, as a manifestation of excyclo torsion during downgaze and encyclo torsion during upgaze. In acute palsy, rapid torsional deviations and slow torsional drifts occur during and immediately after downward saccades. These saccadic intrusions are attributed to pulse-step mismatch, as a result of lesions in the trochlear nerve, which lead to an imbalance of phasic and tonic signals reaching the muscles.

Oscillopsia and Rotary Nystagmus, Synchronous with Heartbeat: A Treatable Form of Nystagmus

First Author: Brian Younge, MD, Rochester, Minnesota

Abstract: Two patients with oscillopsia and a rotary nystagmus synchronous with heartbeat were found in addition to have Valsalva-induced nystagmus. This has been videotaped for presentation. The cause of this was found to be a dehiscence between the superior semi-circular canal and the intracranial cerebrospinal fluid. Surgical treatment of this results in a cure of the nystagmus and oscillopsia.

The Use of Proton Magnetic Resonance Spectroscopy (1H-MRS) to Measure Lactate in the Ocular Vitreous Body in vivo

First Author: Janet Rucker, MD, Atlanta, Georgia

Background: Lactate is present in ocular vitreous at a high level and is increased in ocular pathology, such as retinal ischemia or metabolic diseases. Detection by 1H-MRS of elevated vitreous lactate in vivo would allow a non-invasive evaluation of retinal and optic nerve metabolism.

Objectives: To assess the ability to record a consistent lactate signal with 1H magnetic resonance spectroscopy (1H-MRS) from the vitreous of human eyes in vivo.

Methods: Four normal subjects and one patient with optic neuropathy were included. All 1H-MR spectra were acquired on the vitreous with a 1.5T clinical whole body scanner using a standard head coil. A volume of interest of 1cm³ was placed on the center of the vitreous body. 1H-MR spectra were collected with water suppression. Lactate resonance was assigned by using the chemical shift of water as reference and measuring the J-couple parameter of this resonance.

Results: Lactate was identified as the dominant resonance in each vitreous body tested (at 1.38 ppm chemical shift).

Conclusions: Characterization of the localized MR spectrum of human vitreous in vivo is feasible. We identified lactate as the dominant resonance in the vitreous. Quantification of the
lactate concentration might be possible by utilizing the water resonance as an internal reference. The detection of a reliable lactate peak in the human ocular vitreous is the initial step in application of 1H-MRS to retinal and optic nerve disease.

The Clinical Utility of PET Scanning in the Diagnosis of Essential Blepharospasm

First Author: John Kerrison, MD, San Antonio, Texas

Background: Essential blepharospasm is a disorder characterized by bilateral episodic contractions of the orbicularis oculi muscles and may be difficult to diagnose in its early stages. PET (18fluorodeoxyglucose [18FDG]) neuroimaging in patients with essential blepharospasm has suggested abnormal metabolism in the striatum, thalami, cortical hemispheres, cerebellum, or pons. The value of this test as a clinical tool remains unexplored.

Objectives: The purpose of this study is to assess the potential utility of PET (18FDG) in the diagnosis of essential blepharospasm.

Methods: PET scanning with 18FDG in patients with essential blepharospasm and age/gender-matched controls was performed followed by comparative analysis of the mean count per pixel in several regions of interest.

Results: Analysis of 4 patients with essential blepharospasm and 5 controls demonstrated no differences in the mean count per pixel of the caudate, putamen, striatum, thalami, cortical hemispheres, cerebellum, or pons (t test, 2 tails).

Conclusions: PET (18FDG) neuroimaging does not appear to be clinically useful in the diagnosis of essential blepharospasm.

Inhibitory Mechanisms in Direction Selective Retinal Ganglion Cells that Drive Optokinetic Nystagmus

First Author: Steven Stasheff, MD, PhD Boston, Massachusetts

Abstract: We describe new features of "null inhibition" that help explain the function of direction selective retinal ganglion cells (DSGCs), which generate the earliest visual input driving optokinetic nystagmus (OKN; Oyster et al, 1972). This asymmetric wave of inhibition shadows a moving stimulus on its "null" side (Wyatt and Daw, 1975). We recorded DSGCs in the rabbit retina in vitro while stimulating with single or paired moving bars of light, showing that 1) a bar moving through the receptive field in the preferred direction strongly inhibits the response to a second bar following it; and 2) the spatial extent and duration of this inhibitory wave correspond to prior predictions, to the known spatial and temporal frequency tuning of DSGCs, and to the velocity tuning of OKN. This suggests that the same inhibitory mechanism governs direction selectivity as well as the spatial and temporal response properties of these cells, and hence of OKN. From our experiments, further insights into this inhibitory mechanism include: 1) it is likely postsynaptic; 2) interactions between dendritic layer-specific ON and OFF inputs, activated by leading and trailing edges of moving bars, contribute to null inhibition and likely are mediated by a multistratified amacrine cell; and finally 3) the total amount of inhibition conferred on the cell, measured by probing with a stationary flashing spot, is the same for stimuli moving in the preferred or null direction. Thus, in contrast to classic "integrate and fire" neurons, the DSGC must compute motion direction within local dendritic subunits. A histologic examination of the spatial relationship between excitatory and inhibitory synapses within the dendritic arbor of a DSGC revealed no systematic arrangement (such as alignment of synapses along the preferred-null axis), so identifying the precise nature of local dendritic interactions that mediate this asymmetric inhibition is an avenue for future study.

Anemia and Intracranial Hypertension

First Author: Valerie Biousse, MD, Atlanta, Georgia

Background: Although rarely reported, anemia is considered a classic association with idiopathic intracranial hypertension (IIH). The underlying mechanisms remain unknown.

Objectives: To elucidate the relationship between anemia and raised intracranial pressure (ICP).

Methods: Retrospective case-series and review of the literature. Inclusion criteria included papilledema, neuroimaging ruling-out a space-occupying lesion, and documented anemia.

Results: 3 female non-obese patients with confirmed IIH (normal MRI/MRV, normal CSF, elevated ICP), and 1 male non-obese patient with presumed IIH (normal CT, no LP) were personally evaluated. All had bilateral papilledema associated with peripapillary hemorrhages. 2 had retinal cotton wool spots (CWS), one had retinal hemorrhages. All had severe iron deficiency anemia. Their symptoms/signs improved dramatically after treatment of the anemia. We found 26 well documented cases in the English and French literature. Among those, 9 were excluded from our analyses (8 had confounding disorders, and 1 had cerebral venous thrombosis (CVT)). In the remaining 17 cases, isolated raised ICP associated with anemia was the most likely diagnosis, although in none of these cases was CVT excluded.
There were 13F/4M, mean age 26yo [4–56], 7 were obese; all had bilateral papilledema, associated with CWS in 7, and retinal/preretinal hemorrhages in 10; 10 had chronic headaches, 2 had tinnitus, 4 complained of fatigue, 4 had Vth nerve palsies. LP was obtained in 9 patients (elevated ICP in all; mean 376mm [220–600]). All 17 had severe anemia (mean Hct 18.6% [17–25]) secondary to iron deficiency in 10, B12 deficiency in 2, aplastic anemia in 3, transient erythroblastopenia in 1, and unknown in 1. Treatment included successful reversal of the anemia in all 17, and LP in 9 patients. Visual prognosis was good in 15 patients and unknown in 2.

Conclusions: Anemia may play a role in the occurrence of raised ICP and papilledema. Although only a few cases in the literature support this association, it may be more common than previously thought. Since most patients are not known to be anemic when papilledema is discovered, we suggest that a CBC be obtained in patients with IIH, especially in the absence of known associated factors such as obesity or medications. The underlying mechanisms remain unknown, but CVT should be carefully excluded.

**A Recondite Case of Parinaud Syndrome and Multiple Sclerosis**

First Author: William Lee, MD, Lexington, Kentucky

Abstract: Parinaud syndrome, also known as the dorsal midbrain syndrome or sylvian aqueduct syndrome, may include a combination of the following findings: paralysis of upward gaze, defective convergence, convergence-retraction nystagmus, light-near dissociation, nystagmus, skew deviation, and upper lid retraction. Parinaud syndrome is typically the consequence of mass lesions compressing the tectum. We describe an unusual case in which a solitary midbrain lesion, felt to represent a tectal plate glioma, presented as Parinaud syndrome. On further examination the lesion was determined to represent a demyelinating process heralding multiple sclerosis. We discuss the etiologies and pertinent clinical tests for evaluation of Parinaud syndrome.

**Ocular Toxicity Induced by High-dose Tamoxifen**

First Author: Shlomo Dotan, MD, Jerusalem, Israel

Background: Tamoxifen treatment was associated with refractive crystals in inner retina, macular edema, retinal pigment epithelium abnormalities, optic neuropathy, cataract and vortex keratopathy. The incidence of such ocular toxicity has been reported to be as high as 6.3% in breast cancer patients treated with low doses of tamoxifen. The cumulative levels that could carry an increased risk of toxicity in high-dose treatment are not yet well defined.

Objectives: To assess ocular toxicity of high-dose tamoxifen, a synthetic nonsteroidal antiestrogen drug currently used in high doses for glioblastoma.

Methods: Sixteen patients treated with high-dose tamoxifen (240mg/day) for high-grade brain tumors were included in the study. Six of them were treated for a period of over one year at time of exam. When the periodic ophthalmological examination revealed impaired visual acuity or refractive retinopathy, visual function was further assessed by static perimetry, color vision, full-field and focal electroretinography testing.

Results: Of the six patients treated with high-dose tamoxifen for more than one year, five showed signs of ocular toxicity. The clinical findings included decreased visual acuity, color vision and visual field abnormalities, keratopathy and macular refractive bodies. Full-field electroretinograms (ERGs) revealed impaired rod function, and focal ERGs showed decreased focal cone function in four patients. Ocular toxicity was only partially reversible following the discontinuation of the tamoxifen treatment.

Conclusions: While low-dose tamoxifen treatment has been reported only rarely to cause ocular toxicity, the high-dose treatment of this drug could be the cause of early and frequent signs of toxicity. Baseline ophthalmologic assessment and periodic follow-up exams should be recommended in these patients. Discontinuation of the treatment at the earliest signs of retinal toxicity should be considered, as such changes could be partially reversible.

**Two Cases of Primary HIV Optic Neuropathy**

First Author: Harry O'Halloran, MD, San Diego, CA

Abstract: Two HIV-positive patients presented with optic atrophy of unknown etiology. One, a 27-year-old female, presented with a six-month history of worsening fatigue, weight loss, memory loss, and progressive vision loss in both eyes. The second patient, a 25-year-old male, presented with vision loss and recurrent headaches. These patients are presented in detail with neurologic, ophthalmologic, laboratory, and radiographic findings. In addition, similar cases from the literature are reviewed. We postulate that both patients had a primary HIV optic neuropathy and discuss potential mechanisms of pathogenesis.

**Localization of the Site of Abnormality in Papillo-renal Syndrome**

First Author: Jeffrey Odel, MD, New York, New York

Objectives: To investigate the origin of the visual field defects in two patients with papillo-renal syndrome by recording multifocal electroretinograms (mERG). The
papillo-renal syndrome, inherited autosomal dominantly, consists of bilateral optic disk anomalies associated with hypoplastic kidneys. The optic discs are “vacant” without a central retinal artery but with chorio-retinal vessels exiting the disc. It has been speculated that the visual field defects are retinal in origin (1).

Methods: In both patients, mfERGs were recorded with a bipolar Burian-Allen electrode after the pupil was dilated and the cornea anesthetized. The visual stimulus consisted of 103-scaled hexagons (50° in diameter). One 7-minute run was recorded from OU. The recordings were controlled with VERIS software from EDI.

Results: Both patients had vacant discs with absence of the central retinal vascular system and multiple chorioretinal arteries and were status post renal transplantation. The second patient tested positive for the PAX 2 gene mutation. Both patients had normal intra-ocular pressure. The visual field displayed bi-nasal field loss that crossed the horizontal in the first patient; in the second a nasal defect was present OD and a temporal defect OS. The mfERGs records for both patients were within normal limits OU.

Conclusions: Because the patients’ mfERGs were normal, it is unlikely that they had either a retinal developmental anomaly or had suffered a serous retinal detachment. Given what is known about the cellular origins of the mfERG, it appears that the retinal blood supply is sufficient to maintain normal retinal activity at least up to and including the bipolar cells.

Reference:


The Characterization and Comparison of OHTS Abnormal Visual Field Classifications Using the 24-2 versus the 30-2 Testing Strategies

First Author: John Keltner, MD, Sacramento, California

Background: A classification system was developed for the Ocular Hypertension Treatment Study (OHTS) to describe visual field (VF) abnormalities.

Objectives: To characterize VF abnormalities in OHTS patients and to compare classifications using the 24-2 versus the 30-2 Humphrey VF testing strategies.

Methods: Three certified readers independently classified a subset of 230 (460 hemifields) OHTS abnormal VFs using 17 abnormality classifications. Readers assigned separate classifications to the upper and lower hemifields using the Total and Pattern Deviation probability plots as the primary basis for the classifications. If 2 out of 3 readers agreed, then a final abnormality classification was determined for that hemifield. If 2 readers did not agree, then the VFs were adjudicated by group consensus. After a final classification was made for each hemifield, we compared the 30-2 abnormality classifications with the 24-2 abnormality classifications and determined the frequency and location of differences.

Results: Of the 460 hemifields, 305 (66%) had the same type and location of abnormality using both testing strategies and 155 (34%) had either a different type/location of abnormality or were classified as normal using the 24-2 strategy. Eighty three (54%) of the 155 had a different type/location of abnormality using the 24-2 strategy and 72 (46%) were classified as normal using the 24-2 strategy. Sixty (83%) of the 72 classified as normal using the 24-2 strategy were classified as peripheral defects using the 30-2 strategy. Specifically, these peripheral defects included the following: temporal wedge (19), partial peripheral rim (14), inferior depression (13), superior depression (8), and nasal step (6).

Conclusions: We found the 24–2 testing strategy may reduce artifactual defects, which are evident by the 34% of abnormal hemifields that either had a different type/location of abnormality (18%) or returned to normal (16%). However, it is uncertain how many early glaucomatous defects might be missed.

Cat-scratch Encephalopathy

First Author: Alvin Seah, MD, Atlanta, Georgia

Background: Cat scratch disease is a common cause of ocular disease. It also uncommonly causes an encephalopathy, with variable neuro-imaging findings.

Objectives: To describe a patient with cat-scratch encephalopathy occurring after ocular involvement and to present a review of the literature regarding neuro-imaging findings.

Methods: Single case report and review of the literature.

Results: A 23 year-old woman presented with a branch retinal artery occlusion in the OD. Bartonella titers were elevated at 1:1024 and a course of ciprofloxacin was prescribed. The next month, she reported two nocturnal seizures, a decrease in memory and attention, and clumsiness. A MRI of the brain showed a non-enhancing lesion in the right parietal gray matter with normal DWI, and a repeat Bartonella titer was >1:2048. Of 33 case reports of cat-scratch encephalopathy with reported neuro-imaging findings, 21 had normal neuro-imaging (of which 12 were normal on both CT and/or MRI, and the rest on CT only), and only 12 (36.3%) had abnormal neuro-imaging (5 on CT only and the rest on either MRI alone or both CT/MRI), and
none had gray matter lesions similar to this patient. Various pathophysiologic mechanisms have been proposed in the literature, including direct CNS invasion, host immune response, elaboration of a neurotoxin, and vasculitis.

Conclusions: Cat-scratch disease can manifest as both ocular disease and encephalopathy. Neuro-imaging abnormalities can involve the gray matter.

Effects on Congenital Nystagmus (CN) of Combined Gaze-angle and Vergence Variation: Therapeutic Implications

First Author: Louis Dell'Osso, PhD, Cleveland, Ohio

Objectives: To investigate the observation that once CN is damped by convergence in a binocular subject, it remains damped over a range of gaze angles.

Methods: Ocular motility recordings were made using infrared reflection during fixation of targets at gaze angles varying between ±20° at different values of convergence ranging from far to 20D. The expanded Nystagmus Acuity Function (NAFX) was used to evaluate the CN waveform's relation to potential visual acuity at all fixation points.

Results: During far fixation the subject exhibited a classic null (high NAFX value) with lower NAFX values at gaze angles in both lateral directions from the null. During near fixation, the NAFX values were higher both at the null and at gaze angles to both sides of the null region; that is, the null region was broadened. When plotted for a fixed gaze angle, the variation of NAFX with vergence exhibited hysteresis, being greater during divergence than convergence.

Conclusions: The hysteresis exhibited during vergence implies that the acuity achieved when fixating a target would be higher if one first fixated on a nearer point and then diverged to the target. Damping CN by means of induced convergence, either with base-out prisms or bimedial recession surgery, not only takes advantage of the vergence null (usually stronger than a coexisting gaze-angle null) but also provides a wider range of gaze angles with higher potential acuity. The null-broadening effects of vergence mimic those recently discovered for tenotomy.

Oscillating Scotomas of Migraine Auras or Induced See-Saw Nystagmus (SSN) with Loss of Vertical Fusion in Congenital Nystagmus (CN)

First Author: Louis Dell'Osso, PhD, Cleveland, Ohio

Objectives: To describe and investigate observations made during migraine auras and one episode of loss of vertical fusion in an individual with horizontal-torsional CN.

Methods: Ocular motility recordings were made during fixation of targets in primary position and various amounts of prism-induced vertical diplopia.

Results: Instead of classic migrainous auras, a subject with CN experienced horizontal oscillation (i.e., oscillopsia) of the scintillating scotomas; the other characteristics of the auras were classic. A single, unrelated instance of vertical diplopia produced vertical oscillopsia of one of the two resulting visual fields. During normal fixation of a vertically elongated “+” sign (i.e., a long vertical bar with a short horizontal bar crossing it at its center), neither diplopia nor oscillopsia was perceived regardless of where on the vertical portion of the target the subject fixated. When vertical diplopia was induced (producing two vertically displaced images of the target), oscillopsia occurred. If either the upper or lower horizontal image was fixated, the other appeared to oscillate vertically. If the subject fixated on a point on the vertical bar between the two disparate horizontal images, both images appeared to oscillate vertically in counterphase. Ocular motor recordings revealed an induced SSN that accompanied the loss of vertical fusion.

Conclusions: Classical migrainous auras appear to oscillate in the plane of CN, mimicking the oscillation of a flashed afterimage. In a binocular individual with CN, breaking vertical fusion induced vertical oscillopsia of the non-fixated image or of both images if neither was fixated. The loss of vertical fusion appears to be associated with both induced SSN in CN and the SSN of a chiasma.

A Hypothetical Fixation System Capable of Extending Foveation in Congenital Nystagmus

First Author: Louis Dell'Osso, PhD, Cleveland, Ohio

Objectives: To examine the roles of position and velocity signals in the implementation of a fixation system. This system should act in concert with the smooth pursuit system, allowing the extension of foveation periods by slowing the runaway slow-phase oscillation when position and velocity error fall within given limits.

Methods: The fixation subsystem was incorporated into a robust ocular motor system (OMS) model capable of simulating a multitude of normal responses as well as those made in the presence of abnormalities such as congenital nystagmus (CN), latent/manifest latent nystagmus, gaze-evoked nystagmus, myasthenia gravis, and others. We constructed two candidate fixation subsystems models. The subsystem models were tested first in isolation, verifying their basic functionality. The subsystems were then integrated into the more complex and biologically relevant OMS model, presented previously.
Results: The resulting OMS model demonstrates that foveation duration can be increased to simulate the extended foveation periods commonly observed in complex CN waveforms such as pendular with foveating saccades and pseudopendular with foveating saccades. Only intervals following foveating saccades were extended, not those following braking saccades. This was achieved by monitoring eye position and velocity and providing appropriate control of the commands sent to the OMN.

Conclusions: The OMS model provides possible mechanisms for integrating a fixation system that acts effectively, even in the presence of the high-velocity oscillations of the smooth pursuit system typical in CN. The result is a slowing of the eye during target foveation, creating a more useful period of low-velocity retinal slip that is available to the visual system, this allows for greater visual acuity.

The Fainting Lawyer: A New Cause of Pseudotumor Cerebri

First Author: William Fletcher, MD, Calgary, Alberta

Abstract: A 35-year-old lawyer was referred for assessment of papilledema, which was found incidentally. He felt well generally and had no headache or visual obscurations. Nine months earlier, over a period of four months, he had several episodes of feeling faint, triggered by sitting in a semi-recumbent position. He lost consciousness briefly during three of the episodes but was able to abort most of them by quickly sitting upright. He took no medication. Neuro-ophthalmological and perimetric examination showed normal findings other than bilateral moderate optic disc edema and mild blind spot enlargement. CT scan of the head and orbits was normal. Lumbar puncture revealed an opening pressure of 350 mm. CSF cell counts and protein were normal. MRI and MRV showed no intracranial abnormalities but there was an extracranial, rounded, T2-hyperintense, enhancing lesion, measuring 2 x 2 x 3 cm, located at and below the right jugular foramen. Catheter angiography showed an avascular tumor, which displaced the internal carotid artery and jugular vein. Venous drainage was predominantly through the right transverse, sigmoid and internal jugular veins and there was good venous flow. Extracranial skull base exploration revealed an encapsulated tumor attached to the right vagus nerve. The tumor was removed uneventfully and found to be a schwannoma. Examination two months later showed resolution of the papilledema.

Extracranial tumors rarely cause intracranial hypertension. Papilledema has been reported with involvement of the jugular foramen by metastatic lesions (1) or large glomus jugulare tumors with intracranial extension (2). Rarely, patients with small glomus jugulare tumors present with papilledema (3,4). Vagal schwannoma may cause paroxysmal syncope (5) and should be considered in the differential diagnosis of CT-negative intracranial hypertension, especially for patients who have both conditions.

Coordination of Eye and Head Movement in Parkinson’s Disease

First Author: Paul Wetzel, MD, Richmond, Virginia

Background: Parkinson disease (PD) is a progressive neurologic movement disorder caused by degeneration of dopaminergic cells in the substantia nigra resulting in hypokinesias, rigidity and tremor. The disease can also affect other motor and sensory function including cognitive abilities, contrast sensitivity, color perception and the control of eye movements. Medications can minimize the effects of PD but become less effective as the disease progresses. Deep Brain Stimulation (DBS) employs a stimulating electrode surgically implanted within the globus pallidus or the ventromedial intermediate nucleus of the thalamus to minimize tremor. We conducted a preliminary study of the relationship between eye and head movements of PD patients receiving DBS.

Objectives: To present preliminary data and establish methods to examine the relationship between eye and head movements of PD patients including those with DBS, through the Richmond Veterans Affairs Medical Center, Parkinson’s Disease Research, Education and Clinical Center (PADRECC).

Methods: Over the course of several months we recorded the eye and head movements of one PD patient receiving initially unilateral and then bilateral implantable DBS stimulators. The patient performed fixation and vertical and horizontal visual tracking tasks while unrestricted head and eye movements were measured at 120 Hz using a magnetic head tracking system and a modified pupil-corneal reflection system. Head and eye movements were analyzed for position, velocity, amplitude, duration and gaze.

Results: Head and eye movement data showed random periods of uncorrelated, uncompensated eye and head movements observed during the presence and absence of tremor.

Conclusions: Preliminary results indicate that PD can adversely affect the coordinated relationship between eye and head movement resulting in destabilized gaze control and impaired visual activities.

Doxil Chemomycectomy: 2 Year Results of the Phase 1 Trial

First Author: Jonathan Wirtschafter, MD, Minneapolis, Minnesota
Background: Doxil is a liposome-encapsulated preparation of doxorubicin that is a skin irritant but not a vesicant like the unencapsulated drug. Doxorubicin chemomyectomy is the only proven non-surgical treatment that effects a permanent cure or significant amelioration of essential blepharospasm and hemifacial spasm. Patients who completed the doxorubicin treatment series have been followed for up to 10 years. The median total dose/patient required for cure was 9 mg, although some patients required up to 17 mg. The risk of skin complications significantly limited acceptance of the prior drug.

Objectives: To present the results two years after completion of treatment of the two patients who participated in the Phase I trial of Doxil chemomyectomy for eyelid spasms.

Methods: The two patients received total doses of 24 and 21 mg of Doxil in their upper eyelids with 5 injections/eye and 2 injections into their corrugator muscles within 13 months. Botox rescue treatment of residual spasm was always available and encouraged.

Results: Unlike doxorubicin, Doxil injections in the upper lids always moved immediately into the lower lids. This necessitated a protocol change to limit injections to the upper lids. After completion of the assigned Doxil treatment the mean interval between Botox treatments increased from 91 to 130 days for the high dose patient and from 70 to 128 days for the low dose patient. No complications occurred except for the expected erythematous, which always cleared.

Conclusions: Doxil chemomyectomy has great promise for permanently alleviating or relieving eyelid spasms. Comparing Doxil to doxorubicin, Doxil is much safer for the skin but with at least a 50% reduction in efficacy per mg. The Phase II trial is recruiting patients who will receive total doses of up to 31.5 mg.

Non-arteritic Ischemic Optic Neuropathy in Young Patients Compared with Older Patients

First Author: Ruth Huna-Baron, MD, Tel Aviv, Israel

Objectives: To compare clinical features of patients with nonarteritic anterior ischemic optic neuropathy (NAION) under 50 years of age to older patients.

Methods: Review of medical records of all consecutive patients diagnosed with NAION at Sheba Medical Center and Kaplan Medical Center from 1993–2001. Associated medical conditions, optic disc crowding and second eye involvement were compared between the two groups.

Results: Thirty-three cases under 50 (17%) were found among 198 patients diagnosed with NAION. Age at onset ranged from 22–50 years compared with 50–85 years in the older group. Male predominance was noted in both groups but was higher in the younger group [27/33 (82%)] than in the older group [101/165 (61%)]. Crowded discs were recorded in 55% (18/33) of the younger group compared with 36% (60/165) in the older group, which appeared statistically significant. Hypercholesterolemia was found in 12 (36%) patients of the young cases compared with 43 (25%) of the older cases. Systemic hypertension and diabetes mellitus were more frequent in the older group (47%, 37%; 27%, 27% respectively). Second eye involvement was present in 30% of the younger group compared with 20% in the older group.

Conclusions: NAION is infrequent under the age of 50 and usually requires differentiation from optic neuritis. In our group of younger patients it was associated with known risk factors especially crowded disc and hypercholesterolemia. Second eye involvement was more frequent among the younger patients. Considering that the visual loss event led to the diagnosis of systemic conditions in some of the cases, it seems important to look for these conditions in young patients with NAION.

Long-term Visual Prognosis for Suprasellar (Tuberculum Sellae) Meningiomas

First Author: Carlos Chicani, MD, Baltimore, Maryland

Objectives: To determine the long-term (>10 years) visual and neurologic outcome in patients with suprasellar meningiomas.

Methods: Retrospective case series

Results: Twenty-one patients with suprasellar meningiomas were evaluated. All patients presented with visual complaints. Two patients who were not treated experienced progressive loss of vision in both eyes during follow-up. Among the 19 patients treated, all underwent initial surgery to resect the lesion. The surgery was associated with a 5% mortality rate, an 11% incidence of neurologic morbidity, and a 32% incidence of visual morbidity. Over the follow-up period, seven of the treated patients (37%) developed neuroimaging evidence of either tumor recurrence or growth of residual tumor, with the mean time of 10.7 years. Five of these patients subsequently underwent further surgery, one of whom also received conventional fractionated radiotherapy. Three additional patients received conventional radiation therapy, two shortly after their initial surgery, and one at the time of evidence of recurrent tumor 5 years after initial surgery. Among treated patients, visual acuity initially improved postoperatively in 36% of eyes, remained stable in 47% of eyes, and worsened in 17% of eyes. At final examination, 72% of the patients had visual
A 34-year-old female with a history of Crohn's disease requiring surgical intervention for recurrence of pain had prompted reinstitution of prednisone at least three occasions. Diplopia persisted, and a rheumatology consultation initiated methotrexate with little benefit. Concomitantly, she also had multiple bouts with Crohn's disease requiring surgical intervention for rectovaginal fistula and resection of her ileocolic anastomosis.

Ultimately, due to the severity of her Crohn's outbreaks, even on methotrexate, she was started on Infliximab. After receiving her first dose of Infliximab, she experienced no diplopia for 4 weeks without adjuvant steroids.

Conclusions: This improvement suggests that tumor necrosis factor may play a role in the pathogenesis of orbital pseudotumor. Ultimately, tumor necrosis factor blockers may be useful in the treatment of this inflammatory disease. Further study is warranted to evaluate the effectiveness of this treatment.

A Bayesian Network Model of the Diagnosis of Ocular Myasthenia Gravis: Definition and Practical Significance of a New Decision Support Tool

First Author: Preston Calvert, MD, Alexandria, Virginia

Background: The diagnosis of ocular myasthenia gravis (MG) is often uncertain. Decisions involving invasive diagnostic studies, as well as potentially harmful therapy depend on assessing the likelihood of MG. Bayesian network models allow the conditional probability of a diagnosis to be evaluated in light of the knowledge available about a number of associated clinical findings. Properly structured probabilistic networks help avoid the problems of assuming conditional independence of clinical findings in simpler Bayesian models of diagnosis.

Objectives: A Bayesian network probabilistic model of the diagnosis of ocular MG is presented. Implications for the effective evaluation of a patient with diplopia or ptosis are discussed.

Methods: A systematic review of the clinical, serologic, electrophysiologic, and pharmacologic data that relate to the diagnosis of ocular MG was conducted. A Bayesian network probabilistic model was defined that incorporates the effects of the conditional dependence of related clinical data. Conditional probabilities of the various phenomena in ocular MG were derived from literature sources. Estimates of prior probabilities of phenomena in patients with diplopia or ptosis were estimated from literature sources or the beliefs of an experienced clinician. The effects of various sequences of data elicitation on the posterior probability of ocular MG were evaluated.

Results: Clinical neuro-ophthalmologic findings with high specificity for ocular MG have great value in raising the probability of the diagnosis. Serologic, electrophysiologic, and pharmacologic testing can be structured in a sequence that leads parsimoniously to a high probability of MG, and may spare some suspected MG patients unnecessary invasive testing. Persistent evaluation may lead to a high probability of MG, even when initial results in the diagnostic process are uninformative.

Conclusions: Implementing a Bayesian network model of ocular MG diagnosis may be useful in structuring the evaluation of patients with diplopia or ptosis. Model assumptions...
A Spectrum of Midbrain Tegmental Strokes: Review of 3 Cases

**First Author:** Clifton Otto, MD, Tacoma, Washington

**Background:** Midbrain infarcts are traditionally classified in terms of Benedikt's, Claude's, Nothnagel's, Parinaud's, and Weber's syndromes. While these classifications can be helpful when lesions obey specific boundaries, there are instances where implication of a particular syndrome is imprecise. We present three different cases of ischemic midbrain infarcts with overlapping clinical and radiologic findings.

**Objective:** To present three cases of midbrain strokes with varied clinical and radiologic presentations.

**Methods:** Case reports with discussion of findings and radiologic correlations.

**Results:** The first patient presented with bilateral vertical gaze paresis, a sluggish left pupil and convergence retraction nystagmus suggesting Parinaud's syndrome. However, MRI showed an acute ischemic medial left mesencephalic tegmental infarct involving the red nucleus with extension into the thalamus suggestive of Claude's or Benedikt's syndromes. The second patient presented with fluctuating mental status, normally reactive pupils, and absence of vertical gaze again suggesting Parinaud's. By contrast, the MRI showed acute infarction of the rostral left paramedian mesencephalon, left cerebral peduncle, and ventral thalamus consistent with Weber's or Benedikt's. The third patient presented with depressed mental status, dysarthria, bilateral ptosis, and a right third nerve paresis suggestive of a central tegmental lesion. MRI showed an acute infarct of the caudal right paramedian mesencephalic tegmentum extending into the cerebral peduncle once again suggestive of Weber's or Benedikt's.

**Conclusions:** Midbrain lesions may not always respect the boundaries of the traditional midbrain syndromes. In the three cases presented signs and symptoms did not coincide precisely with the radiologic findings. This may be explained by individual anatomic variations, pre-existing ischemic brain injury, incomplete understanding of neuroanatomic pathways, and by improved definition of anatomic lesions due to advancements in neuro-imaging techniques.

Optic Neuropathy after LASIK

**First Author:** Wayne Cornblath, MD, Ann Arbor, Michigan

**Background:** Laser in situ keratomileusis (LASIK) is an increasingly common ophthalmic procedure done to correct myopia, hyperopia and astigmatism. Most complications relate to creation of the flap or are optical in nature, glare etc. Optic neuropathy has rarely been reported as a complication of LASIK.

**Objectives:** Report 3 cases of LASIK induced optic neuropathy, review the literature and discuss possible mechanisms of injury.

**Methods:** Case report.

**Results:** 3 patients were seen at 3 academic centers with unilateral optic neuropathy occurring 1–7 days after otherwise uneventful LASIK surgery. One patient had a long history of migraine. All patients had afferent pupillary defects and visual field defects, with varying levels of visual acuity and fundoscopic appearance. There was some improvement
over time in either visual field or acuity in 2 patients. Evaluation for other causes of optic neuropathy was negative.

Conclusions: Optic neuropathy is a rare occurrence after LASIK. Possible mechanisms include ischemia to the nerve during suction or mechanical trauma. In one patient, migraine might have been an additional risk factor.

Extracocular Extension of Choroidal Melanoma Mimicking Primary Optic Nerve Tumor

First Author: Dan Boghen, MD, Montreal, Quebec

Background: Juxtapapillary choroidal melanoma with extracocular extension presenting as a primary optic nerve tumor

Objectives: To report the unusual presentation of an unrecognized juxtapapillary choroidal melanoma with extracocular extension mimicking a primary optic nerve tumor.

Methods: Case report with review of clinical, radiologic and histopathologic records.

Results: A patient presented with signs of compressive optic neuropathy and disk edema. CT scanning, magnetic resonance imaging and B-scan ultrasonography initially pointed toward a primary optic nerve tumor. Subsequent fundus examination disclosed a juxtapapillary pigmented choroidal lesion. The patient underwent enucleation with a long optic nerve section. Histopathologic analysis confirmed the diagnosis of a small juxtapapillary choroidal melanoma with extracocular extension within the meninges compressing the optic nerve.

Conclusions: Although extracocular extension of choroidal melanoma usually occurs in eyes with medium or large intraocular tumors, it can also originate from small, unrecognized juxtapapillary tumors, thus mimicking a primary optic nerve lesion.

Acute Ophthalmoplegia and Mydriasis Associated with IgG Anti-GQ1b Antibody

First Author: Lee Snyder, MD, Baltimore, Maryland

Background: The presence of IgG anti-GQ1b antibodies has been associated with the ophthalmoplegia and ataxia seen in the Miller Fisher and Guillain-Barré Syndromes. More recently, patients with variants of the MFS clinical triad with ophthalmoplegia, but without ataxia and areflexia, have been described.

Objectives: To report a case of acute ophthalmoplegia and mydriasis associated with IgG anti-GQ1b antibody.

Methods: Observational case report and literature search.

Results: A 17-year-old college student with a history of a febrile illness one month prior to presentation noted a rash involving her extremities and trunk. Within two days of the onset of the rash, she developed photophobia and paresthesias involving her extremities, and she was noted to have dilated pupils. Five days after the onset of the rash, she awakened with bilateral horizontal diplopia. Ophthalmologic examination revealed visual acuity of 20/25 in OU, bilateral dilated pupils that were nonreactive to light or accommodation, a 15 prism diopter esotropia at distance, and bilateral limitation of supraduction and abduction. The optic nerve and retina were unremarkable. Neurologic examination showed normal motor and sensory function with intact reflexes and no gait abnormalities. A work-up included a lumbar puncture, which was within normal limits and an MRI significant for incidental sinusitis. A blood test was positive for IgG and IgM against Epstein-Barr viral antigens as well as for elevated GQ1b autoantibodies.

Conclusions: The presence of a common autoantibody in MFS and GBS as well as clinical variants of the two suggests a related autoimmune etiology. This case falls along the spectrum of clinical findings associated with GQ1b antibodies and may be related to a recent infection with the Epstein-Barr virus.

A Case of Sudden Monocular Loss of Accommodation

First Author: Mark Gans, MD, Montreal, Quebec

Abstract: A 40-year-old male presented with sudden “blurring” of his OD for near and distance viewing. The visual loss was stable since its onset 4 weeks prior to presentation. There was no pain on eye movement or any other associated neurologic symptoms. He did not have any significant medical, neurologic, surgical or traumatic history. He had a “pleomorphic adenoma” removed from his right submaxillary gland. There was no recurrence. On examination his vision was correctable to 20/25 O.D. (-6.25 + 1.25 x 80) and 20/20 O.S. (-6.5 + 1.25 x 80). With his distance correction in place he was able to read J1 with the OS but required a +2.5 diopter lens to read J1 print held at 30 cm with the OD. Pupils were 6mm each and both were briskly reactive to light and accommodation. The rest of the examination was within normal limits. The Humphrey 30–2 was normal in the OS and demonstrated a “general reduction” in the OD. An initial CT and MRI of the brain were interpreted as normal. A UBM was performed and demonstrated a 360 degree calcific band within the ciliary body of his OD. The OS demonstrated an incomplete calcific band in the ciliary body. A repeat CT of the orbit confirmed the presence of these calcifications. The patient’s internist was unable to detect any calcium metabolism abnormality.
The Use of Contact Lenses to Treat Visually Symptomatic Nystagmus

First Author: Valerie Biousse, MD, Atlanta, Georgia

Background: Nystagmus degrades vision by disrupting fixation. CL may improve visual function of patients with nystagmus by 1) correcting the patient’s refractive error better than spectacles; 2) by dampening the nystagmus itself through sensory feedback from movement of the CL against the cornea/lids as the eyes oscillate.

Objectives: To determine the effects of contact lens (CL) wear on visual function of patients with visual loss from congenital nystagmus.

Methods: 4 patients with congenital nystagmus (3M, IF, age 18–64) were included. All patients underwent complete ophthalmologic and neurologic examinations. Each patient had two evaluations separated by at least one week (one with spectacles, one with CL) including best corrected visual acuity (BCVA), contrast sensitivity, oscillophsia scale, quality of life questionnaire (NEI VFQ-25), and eye movement recording (infrared eye tracker at a sampling rate of 1000 Hz).

Results: 2 patients had congenital motor nystagmus and 2 had albinism. All had refractive errors primarily corrected by spectacles and CL (BCVA: 20/40–20/100). All were fitted with soft CL (diam 8.2–14.5 mm). All patients subjectively preferred CL to spectacles. Their visual acuity, contrast sensitivity, and VFQ-25 scores were improved with CL compared with spectacles alone. Eye movement recording (frequency mean, peak amplitude, peak velocity, foveation time) showed no change in 2 patients, worsening in 1 patient and improvement in 1 patient.

Conclusions: This small sample of patients suggests that, in addition to a placebo effect from CL wear, much of the clinical improvement observed in our patients may result from a better optical correction of their refractive error with CL than with spectacles, rather than from a true dampening effect of the nystagmus by CL. More patients are currently under investigation.

Ocular Ischemic Syndrome Following Occlusion of Both External Carotid Arteries

First Author: Adeela Alizai, MD, Ann Arbor, Michigan

Background: Ischemic oculopathy and orbitopathy have often been reported in association with common carotid artery occlusive disease. The ischemia has been attributed to reduced flow through the internal carotid artery and its tributary, the ophthalmic artery. Yet the external carotid artery is often the principal source of blood flow to the orbit and eye. Curiously, orbito-ocular ischemic syndromes have not been reported in association with occlusion limited to the external carotid artery.

Objective: To demonstrate the fact that isolated occlusion of both external carotid arteries can cause ischemic damage to the eye, orbit, and ocular motor nerves and to emphasize that such isolated external carotid artery occlusion may occur following carotid endarterectomy.

Methods: Two case reports.

Results: Case I is a 70-year-old woman who developed OS visual acuity loss, ipsilateral periorcular pain, venous stasis retinopathy, iris neovascularization, and seventh nerve palsy one year after sequential carotid endarterectomies. Cerebral angiography demonstrated patent common and internal carotid arteries bilaterally, but complete occlusion of both external carotid arteries and no flow in the left ophthalmic artery. External carotid artery patch grafting and stenting restored flow through the ophthalmic artery, reversed the pain, did not reverse the ocular ischemic findings, and precipitated neovascular glaucoma. Case II is a 70-year-old man spontaneously developed right ischemic optic neuropathy, corneal edema, ipsilateral ocular motor palsies and later contralateral ischemic optic neuropathy. Cerebral angiography showed partial atherostenosis of both internal carotid arteries (right much greater than left), absent flow in the right ophthalmic artery, and bilateral external carotid artery occlusions.

Conclusions: Bilateral external carotid occlusion, in conjunction with atherostenosis of the internal carotid artery, can cause ocular, orbital, and ocular motor ischemia. Surgeons should beware of occluding the external carotid artery during endarterectomy of the internal carotid artery.

To Sleep, Perchance to Breathe: a Case Report

First Author: Renee Bailey, MD, San Antonio, Texas

Abstract: A 38-year-old welder had visual loss, disc edema, and retinal hemorrhages as the presenting features of obstructive sleep apnea (OSA). General physical examination revealed height 6 feet 8 inches, weight 159 kg. BP 118/87. Ophthalmologic examination demonstrated VA 20/60 OD, 20/400 OS, visual fields with enlarged blind
spots with arcuate depression OU, equally reactive pupils with no afferent defect, normal ocular motility, dramatic optic disc edema, exudative maculopathy, nerve fiber layer hemorrhages on and adjacent to disc with additional pre-retinal hemorrhages. MRI and MRV of the brain were normal. CSF examination was normal with an opening pressure of 250 mm H2O. Polysomnogram performed the following night revealed repeated apnic spells and arousals every one to 2 minutes during stage 2 sleep and associated oxygen saturation between 50% and 70%. CPAP was titrated to 12 mmHg, and the patient subsequently achieved stage 4 sleep, with only 2 subsequent arousals. The patient received home CPAP and was followed for 8 months, after which time he was lost to follow-up. His final examination demonstrated VA 20/80 OD, 20/25 OS, disc edema had improved somewhat OU with resolution of hemorrhages. The maculae continued to exhibit exudative changes. OSA is a common disorder, neurologically often presenting with headache, hypertension and stroke. Although the association of OSA and disc edema has been previously described, disc edema appears to be a relatively infrequent complication. This association may be under-reported, and better data about visual loss in sleep-disordered breathing, the influence of hypertension, and identification of high-risk sub-populations are needed.

Light Sensitivity in Patients with Blepharospasm

First Author: Wesley Adams, MD, Salt Lake City, Utah

Background: Benign essential blepharospasm is a movement disorder characterized by excessive blinking and involuntary closure of the eyelids. That light would have something to do with blepharospasm should be expected. Patients often report their spasms to be triggered and exacerbated by light sensitivity both to ambient light and bright lights. In fact, in many series bright light is the most common exacerbating factor in almost 80%, followed by dry eye syndrome (49%), eye irritation (55%), and eye pain (31%). Some combination of these symptoms is reported in 64%. Light sensitivity has never been systematically studied in this group of patients.

Objective: To compare light sensitivity in patients with blepharospasm, patients with known photosensitivity (migraine), and patients without blepharospasm or migraine.

Methods: We prospectively examined 24 control patients, 30 patients with blepharospasm, and 29 patients with migraine headaches. Light sensitivity was studied by exposing patients to a bright, white, halogen light source. Luminance was measured with a portable light meter. The light was gradually increased in intensity by graduated steps until the patient reported discomfort. Each measurement was performed three times. Patients were then retested using photo-gray and FL-41 (rose-tinted) spectacles.

Results: We found that the groups with blepharospasm and migraine both were more photosensitive than the control group. As expected, tinted spectacles increased thresholds for discomfort in all groups. Even with tinted spectacles, the migraine and blepharospasm groups were still consistently more light-sensitive than the controls. Although there was a trend for the FL-41 tint to be more effective than the photo-gray, the difference was not statistically significant.

Conclusions: In summary, patients with blepharospasm have a lower threshold for light sensitivity than patients without blepharospasm. Light sensitivity in patients with blepharospasm is similar to that found in migraineurs. Tinted spectacles are helpful in reducing light sensitivity symptoms. We recommend that light sensitivity be addressed in patients with blepharospasm and that the clinical efficacy of tinted spectacles be studied in future investigations.

Migraine and Blood Pressure Relationships: Funduscopic Features

First Author: Ernesto Rios-Montenegro, MD, Lima, Peru

Background: Funduscopic features of migraine are not well defined and their correlation with blood pressure has not been established.

Objectives: To display the funduscopic changes of different types of migraine and to show at the same time their relation to blood pressure, allowing us to infer the type and amount of ensuing hypertension.

Methods: Observational. Fundus characteristics of classic, acephalgic and common migraine were compared during intercritic periods. Blood pressure was obtained and correlated with the funduscopic features of each type of migraine.

Results: Classic migraine has features between those of acephalgic and common migraine. In acephalgic migraine the retinal arteries are narrow and the retinal nerve fiber layer (RNFL) has normal appearance. When these narrow arteries sclerose diastolic hypertension ensues, with a resulting short differential or pulse pressure. It corresponds to adrenergic or type A personality subjects and eventually may lead to earlier ischemic events or multiple small infarcts. On the other hand, in common migraine the retinal arteries are wide and the appearance of the RNFL is peculiarly enhanced, as manifested by accentuation of the retinal peripapillary striae. When these arteries sclerose, they lead primarily to systolic hypertension. These people have a vagotonic or type B personality and they are prone to develop large brain infarcts and hemorrhages. In classic
migraine the funduscopic characteristics are indistinguishable from those of normal or non-migraine people. When their arteries harden, they more likely will develop mixed or global (systo-diastolic) hypertension.

Conclusions: Migraine is not synonymous of headache and should not be referred only to the period of crisis. Funduscopic features during intercritical intervals allowed us to differentiate three main groups of migraine: acephalgic, classic and common. The predominant influence of adrenergic or vagotonic substances seem to be responsible for the funduscopic vascular changes as well as for the personality trait for each group of the affected individuals. Upon development of arteriolosclerosis, the appearance of the neuroretinal vessels correlate with the type and severity of ensuing hypertension, whether primarily diastolic, systolic or systo-diastolic, as well as with the eventual development of corresponding vascular complications, particularly at the nervous and cardiac systems.

Optic Radiation Involvement in Optic Pathway Gliomas AND Neurofibromatosis

First Author: Grant Liu, MD, Philadelphia, Pennsylvania

Background: Optic pathway gliomas (OPG, pilocytic astrocytomas) in NF-1 typically involve some combination of the optic nerves, chiasm, or optic tracts. Involvement of the optic radiations is only rarely recognized (1).

Objective: To report five patients with neurofibromatosis type 1 (NF-1) with gliomas involving the pregeniculate optic pathway and also the optic radiations.

Methods: Database review of all patients with NF-1 and optic pathway gliomas seen by GTL at the Children's Hospital of Philadelphia (CHOP) from July 1993–October 2001. Patients with involvement of pregeniculate optic pathway and the optic radiations were identified. Cases were also identified from the practice of MCB at Arkansas Children's Hospital (ACH).

Results: Four patients from CHOP (out of 83 total NF-1/OPG), and one from ACH were identified. Three had expanding mass lesions within the white matter of the temporal or parietal lobes, which were pathologically demonstrated to be pilocytic astrocytomas. The other two had radiographic involvement of the optic radiations, but did not undergo biopsy. In all five cases the vision was 20/200 or worse in OU, but the visual loss could usually be attributed to the pregeniculate involvement.

Conclusions: Neuro-ophthalmologists should be aware that OPGs in NF-1 may involve the optic radiations, and in such patients the vision is usually severely affected. While the additional optic radiation lesions may not necessarily lead to further vision loss, the poor vision in such patients may simply reflect the relatively poorer visual prognosis of OPGs with retrochiasmal involvement in patients with NF-1 (2).

References:
Upcoming Meetings

June 18–22, 2002
Canadian Congress of Neurological Sciences Annual Meeting
Vancouver, BC, Canada
http://www.ccns.org
Contact: congress@venuewest.com

June 26–29, 2002
The XV International Perimetric Society (IPS)
Stratford-Upon-Avon, UK
Contact: (01) 491-579-058
carolyn@delegate.uk.com

July 7–12, 2002
10th International Congress of Neuromuscular Diseases
Vancouver Convention and Exhibition Center
Vancouver, BC, Canada
http://www.venuewest.com/icnmd2002/
Contact: (604) 681-5226
congress@venuewest.com

July 7–9, 2002
25th Annual Meeting of the Japanese Neuroscience Society
Tokyo, Japan
http://www.jnss.org/page/English/

October 2–5, 2002
Joint European Research Meeting in Ophthalmology and Vision
Palacio de Congresos del Colegio Oficial de Medicos
Alicante, Spain
http://www.ever.be
Contact: secretaria@ever.be

October 13–16, 2002
American Neurological Association
Marriott Marquis
New York, NY
http://www.anneuroa.org/annual.htm
Contact: lorijanderson@msn.com

October 18–20, 2002
40th Annual Meeting of the Japanese Neuro-Ophthalmology Society
Tokyo, Japan
Contact: (81) 353-633-821

October 20–23, 2002
American Academy of Ophthalmology Annual Meeting
Orlando, FL
http://www.aao.org/aaweb1/Meetings/139_1645.cfm
Contact: meetings@aao.org

November 2–7, 2002
Society for Neuroscience Annual Meeting
Orlando, FL
http://www.sfn.org/
Contact: info@sfn.org

February 8, 2003
Frank B. Walsh Meeting
Snowbird, UT
http://www.nanosweb.org/meetings/
Contact: (860) 586-7507 x533

February 9–13, 2003
Snowbird, UT
http://www.nanosweb.org/meetings/
Contact: (860) 586-7507 x533

March 7–10, 2003
American Society of Neuroradiology Annual Meeting
New Orleans, LA
http://asnr.org/annual/futuremeetings.html

March 28–April 1, 2003
XXIV Pan American Congress of Ophthalmology
San Juan, Puerto Rico
http://www.panamofta2003.org
Contact: info@paao.org

March 29–April 5, 2003
American Academy of Neurology (AAN)
Honolulu, Hawaii
http://aan.org/future.htm

April 2–6, 2003
American Academy of Ophthalmology Mid-Year Forum
Renaissance Mayflower Hotel
Washington, DC
http://www.aao.org/aaweb1/Meetings/145.cfm

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May 4–9, 2003
The Association for Research in Vision and Ophthalmology (ARVO)
Fort Lauderdale, FL
http://www.arvo.org/

June 15–18, 2003
European Neuro-Ophthalmological Society (EUNOS)
Goteborg, Sweden
Contact: bertil.lindblom@neuro.gu.se