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Driving a motor vehicle is the primary and preferred mode of travel for adults in many countries around the world. It is hard for many of us to imagine life without the use of an automobile. Probably not well known is the fact that driving has a widespread impact on health and well-being. Driving cessation has been linked to many negative outcomes, including increased likelihood of depression and social isolation (1), reduced access to health care services (2), and increased risk of entry into long-term care (3).

Controlling a vehicle is obviously a highly visual task involving visual sensory functions, such a spatial resolution, contrast sensitivity, and light sensitivity. Yet by themselves, visual sensory functions are insufficient for safe driving performance. Driving goes beyond visibility issues and depends on the time-sensitive gathering of visual information used to support decision making and motor behaviors. Controlling a vehicle takes place in a visually cluttered environment with many distractions and involves the simultaneous use of central and peripheral vision. As the vehicle moves through the environment, the visual world is rapidly changing. The driver is often uncertain as to when and where a critical event will occur. Thus, it should not be surprising that research to date (4) indicates that the most effective vision-screening test for identifying crash-prone drivers is not a visual sensory test but a visual processing speed test with divided attention components. As Johnson and Wilkinson (5) point out in this issue of the Journal, the useful field of view test, which embodies these stimulus and task components, shows great promise as a method for visually screening older drivers at high risk for automobile collisions. Studies are currently underway to establish its efficacy in large populations in screening and rescreening older drivers for licensure (6).

Jurisdictions throughout the world have recognized the importance of enhancing public safety on the roadways, and in so doing, set requirements for obtaining a driver’s license. Visual acuity is the most common method for vision screening for licensure. Yet, as Yazdan-Ashoori and ten Hove (7) point out in this issue of the Journal, there is wide variability in the level of visual acuity required to pass a licensure test. This lack of uniformity is understandable since there is no scientific evidence indicating what visual acuity cut-point for a screening test is most effective. In setting a visual acuity standard, jurisdictions are left to historical precedent, consultation with “experts” or policy advocates, public opinion, and/or reliance on the fact that sight distances for highway signs are designed for drivers having at least 20/30 Snellen binocular visual acuity (8). What is needed are well-designed, population-based, prospective studies to establish the association between visual acuity and incident at-fault motor vehicle collision involvement. Such studies would provide the necessary data not only to establish predictive acuity cut-points for at-risk drivers but also whether any acuity cut-point provides predictive validity to enhance highway safety. Future research might also examine how visual acuity screening could be supplemented with other screening techniques such as contrast sensitivity, processing speed, and divided attention tests, which have a growing evidence basis for their relevance to driver safety (5,7,9).

The ophthalmologist is often called on to render an opinion regarding driving safety in a patient with impaired vision. The patient or family members may have described incidents that prompt concerns about the patient’s own safety and the safety of other drivers and pedestrians. As Johnson and Wilkinson (5) and Yazdan-Ashoori and ten Hove (7) point out, some states and provinces have mandatory
reporting laws. In the absence of such laws, professional societies such as the American Medical Association must remind physicians of the ethical responsibility they have in reporting at-risk drivers. There are several dilemmas here. Some physicians do not know what the vision standard is for their state. Most physicians may not be aware of their state’s reporting laws or how to go about issuing such a report. And what are the legal protections for the physician in terms of patient privacy issues versus the duty to protect the well-being of the community? A great deal of continuing medical education is required here, and it should be done at the state or provincial level given the significant policy differences across these jurisdictions. Finally, lacking the necessary training and expertise, physicians often feel uncomfortable in making such decisions, which will have major consequences for patients and their families.

Recently, driving assessment and rehabilitative services have emerged within the United States and Canada, which are staffed by occupational therapists and/or certified driving rehabilitation specialists. These professionals have the educational background and experience to evaluate the potential for safe driving in persons with functional impairments. Rather than risk making an inappropriate recommendation to stop driving, or telling a patient that it is “ok to drive,” physicians now have the option to refer patients to these driving clinics for appropriate assessment. Unfortunately, in most instances, these driving fitness evaluations are not yet covered by health insurance and will be an out-of-pocket expense to the individual.

Although the number of driving assessment and rehabilitation clinics is increasing and driver rehabilitation is recognized as a subspecialty within occupational therapy, there are widespread differences in preferred practice standards for both assessment and rehabilitation. Once again, this stems from a lack of evidence-based research to determine the best predictors for future collision involvement and what visual and cognitive skills are critical for good driving performance. Comparative effectiveness studies can tackle these problems to determine whether the driving assessment clinics are efficacious as compared to the traditional approach of physician reporting to the licensing office.

So the bad news is that there is much to learn about what the visual and eye condition risk factors are for unsafe driving, what screening tests are best with what cut-points for identifying at-risk drivers, and what assessment and rehabilitation strategies have good patient and societal outcomes. However, the good news is that these are all fundamentally researchable questions that can be practically addressed with current clinical trial and epidemiological study designs and measurement techniques. All it takes now is the societal commitment to identify the financial resources to underwrite the research to address these questions, whose answers will impact the health and well-being of millions of drivers worldwide.

REFERENCES
Abstract: A 52-year-old man with chronic hepatitis C presented with painless, bilateral, simultaneous non-arteritic anterior ischemic optic neuropathy (NAION) and peripheral neuropathy. Symptoms began 19 weeks after starting peginterferon alpha-2a. The peripheral neuropathy and vision of the right eye improved, but the vision of the left eye worsened after stopping interferon. We identified 23 additional cases of NAION during interferon alpha therapy. At least 12 of these patients suffered bilateral NAION. Patients lost vision 1–40 weeks after initiating therapy. Of 21 eyes that had documented initial and follow-up acuities, 8 improved, 1 worsened, and the rest remained stable. One patient had a painful peripheral neuropathy. Treatment with interferon alpha may result in NAION. Discontinuation of therapy deserves consideration after weighing individual risks and benefits.

doi: 10.1097/WNO.0b013e3181d8e4af
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Interferon alpha is a complex glycoprotein with antiproliferative, antiviral, and immunomodulatory activity (1). Pegylated interferons have a covalently attached 40 kDa branched chain polyethylene glycol moiety, which improves drug absorption and prolongs the half-life from 4 to 22–60 hours (2), allowing for less frequent injections and improved patient compliance. The 2 forms of pegylated interferon alpha currently approved for the treatment of chronic hepatitis C (CHC) are peginterferon alpha-2a and peginterferon alpha-2b. While peginterferon alpha-2b has a larger volume of distribution and more effective renal clearance than peginterferon alpha-2a (3), studies have found no difference in either the sustained virological response or adverse event incidence between the 2 medications in the treatment of CHC (4).

The most common adverse events associated with interferon alpha therapy are flu-like symptoms, leukopenia, thrombocytopenia, depression, and thyroid disorders (5). Cases of peripheral neuropathy have also been documented (6–10). Several prospective studies have linked interferon alpha therapy with a high incidence of retinopathy, demonstrated by the presence of cotton wool spots and hemorrhage (11–19), although these changes are often asymptomatic (12,16). Other documented ocular complications of interferon alpha therapy include transient blurred vision (20), increased intraocular pressure (21), neovascular glaucoma (22), retinal detachment (5), and orbital and intraocular hemorrhage leading to enucleation (21,23). Nonarteritic anterior ischemic optic neuropathy (NAION) is a relatively rarely reported complication of interferon alpha therapy (15,24–40).

We present a case of NAION following treatment of CHC with peginterferon alpha-2a and review the literature for other documented cases of NAION following interferon alpha therapy.

CASE REPORT
A 52-year-old man with a history of CHC developed painless progressive vision loss in his right eye. He did not detect visual loss in the left eye. He also noted new onset numbness and tingling in both hands and feet. He denied symptoms suggestive of giant cell arteritis. His medical history included migraine headache, cervical radiculopathy, depression, anxiety disorder, and insomnia. Nineteen weeks prior to ophthalmic evaluation, he began treatment for CHC with peginterferon alpha-2a 180 μg/week and
Ribavirin 1000 mg/day. Other medications included filgrastim, albuterol, eletriptan hydrobromide, hydromorphone, fluticasone and salmeterol, bupropion, clonazepam, omeprazole, zolpidem, prochlorperazine, and tizanidine.

Two days later, examination revealed vision of 20/25 in each eye. Pupils were 3 mm bilaterally with a right relative afferent pupillary defect (RAPD). The patient correctly identified all of the Ishihara color plates with each eye. Fundus examination demonstrated bilateral optic disc edema (Fig. 1) with a normal appearance to each retina. Fundus photographs from 2003 revealed a cup-to-disc ratio of 0.1:0.2. Visual field testing demonstrated inferior field loss in the right eye and no abnormality in the left eye (Fig. 2).

Contrast-enhanced MRI of the brain and orbits showed no optic nerve or intracranial abnormalities. Lumbar puncture demonstrated a normal opening pressure, with normal protein and glucose levels; no white blood cells; and 32 red blood cells. Hemogram showed mild pancytopenia with a white blood cell count of 1800 cells per microliter, platelet count of 110,000 cells per microliter, and hemoglobin of 13 g/dL. A comprehensive metabolic panel showed no abnormalities. Antinuclear antibody, angiotensin-converting enzyme, rapid plasma regain, and neuromyelitis optica (NMO) IgG testing were all negative.

Both peginterferon alpha-2a and ribavirin were discontinued. The patient received intravenous solumedrol 500 mg followed by oral prednisone 40 mg, which was tapered over the next 8 days. When examined 4 weeks later, he reported a 4-day decline in vision in his previously asymptomatic left eye and some improvement in his right eye. Visual acuity was 20/20 in the right eye and 20/60 in the left eye. He saw 8/8 Ishihara color plates with the right eye and 3/8 with the left eye, and there was no evidence of a RAPD. The right optic nerve showed early segmental atrophy while the left optic nerve swelling had worsened. Visual field testing demonstrated slight progression of the inferior arcuate scotoma in the right eye and a new defect in the left eye (Fig. 3). The patient noted almost complete resolution of his paresthesias.

**DISCUSSION**

Our patient suffered bilateral simultaneous NAION in the setting of peginterferon alpha-2a treatment. Spontaneous, bilateral, simultaneous NAION is rare and typically suggests a systemic disorder or toxicity. While it is conceivable that the interferon therapy was unrelated, this seems unlikely since this case has similar findings to previous reports. In addition, our patient had bilateral paresthesias of the hands and feet, a known side effect of pegylated interferon alpha. With discontinuation of therapy, he noted near total resolution of this symptom, strongly suggestive of a systemic toxic effect of his interferon therapy.

We are aware of 23 additional cases of NAION in the setting of interferon alpha therapy (Table 1). Eleven patients experienced bilateral NAION. One probable case of NAION following interferon alpha-2b therapy for CHC and one following interferon alpha-2a therapy for acute hepatitis C were omitted from this compilation because the abstracts were not available in English. All other reported patients suffered visual loss between 1 and 40 weeks after initiating therapy. Thirteen cases received combination therapy with ribavirin and interferon alpha. Of these 13 patients, 6 experienced bilateral visual loss. Four patients suffered NAION while taking interferon alpha-2a and 7 while taking interferon alpha-2b. Eleven reports only described treatment as “interferon alpha” therapy. Of these 11 patients, 4 experienced bilateral optic nerve involvement. There was one documented case of NAION following therapy with natural (nonrecombinant) interferon alpha. Of the 17 cases that provided follow-up information, 9 described improvement in signs and symptoms following cessation of interferon alpha, and one showed symptomatic improvement without the withdrawal of therapy. One patient developed painful polyneuropathy in addition to NAION.

How interferon causes NAION is currently unknown. Sugano et al (44) studied patients who developed retinopathy while taking interferon alpha (49). They discovered abnormally high levels of circulating activated plasma complement.

**FIG. 1.** Bilateral optic disc edema is present with a flame hemorrhage (arrow) on the left eye.
5 (C5a), an intravascular aggregator of granulocytes. High C5a levels may disrupt blood flow in the retinal circulation, leading to retinal capillary infarction, cotton wool spot formation, and hemorrhage (48,49). Guyer et al (16) proposed that therapy with interferon alpha may cause autoantibody formation and immune complex deposition, with resultant lymphocyte infiltration and inflammation of vessels, leading to retinal ischemia. Nishiwaki et al (50) used a rat model to demonstrate that interferon alpha causes leukocyte activation and adherence to vascular endothelium. The mechanisms proposed for interferon alpha–associated retinopathy could also underlie the development of NAION, with involvement of the posterior ciliary arterial circulation, leading to optic nerve ischemia (26).

It is unlikely that the coadministration of ribavirin contributes directly to the development of NAION, as the only known ocular complication of ribavirin therapy is conjunctivitis. Presumably, this occurs from topical irritation of the conjunctiva, as conjunctivitis only follows aerosol administration (51).

Hepatitis C virus (HCV) has been linked to various immunologic abnormalities, including cryoglobulinemia, arteritis, and thrombocytopenia (52). It appears unlikely that the virus itself was the cause of NAION in our patient, as there was no evidence of systemic vasculitis. While our patient did have thrombocytopenia, Hayasaka et al (13) found no association between thrombocytopenia and ocular complications in patients with CHC receiving interferon therapy. Additionally, development of NAION due directly to HCV infection is extremely rare, with only 2 cases documented (53,54).

Our patient had a preexisting small cup-to-disc ratio, a proposed risk factor in the development of NAION (42). One previous report of unilateral NAION associated with pegylated interferon noted a small optic disc in the fellow eye with crowding and absence of cupping (32). Two other cases of bilateral NAION documented absence of physiologic cupping in the fellow eye prior to second eye involvement (26). It is conceivable that a small cup-to-disc ratio may increase the risk of NAION in patients receiving interferon alpha.

Based on the evidence from our patient, as well as from the compiled case reports, we propose that the association between interferon alpha therapy and the development of NAION is “possible,” based on the World Health Organization criteria for establishing causality in adverse drug reactions (Table 2) (http://www.who-umc.org/DynPage.aspx?id=22682). The visual changes consistent with

![FIG. 2. Initial visual fields show an inferior arcuate defect in the right eye and a normal result in the left eye.](image)

![FIG. 3. Four weeks later, visual fields reveal slight progression of field loss in the right eye and an inferior altitudinal defect with central involvement in the left eye.](image)
<table>
<thead>
<tr>
<th>Patient Age, Gender (reference)</th>
<th>Underlying Disease</th>
<th>Medication</th>
<th>Unilateral vs Bilateral</th>
<th>Treatment Duration Prior to NAION</th>
<th>Visual Acuity at Presentation</th>
<th>Visual Acuity After IFN Cessation</th>
</tr>
</thead>
<tbody>
<tr>
<td>54, Female (37) CHC</td>
<td>IFN alpha-2a, ribavirin, and amantadine</td>
<td>Bilateral</td>
<td>6 months</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>68, Female (25) CHC</td>
<td>IFN alpha-2a and ribavirin</td>
<td>Unilateral</td>
<td>3 weeks</td>
<td>20/50</td>
<td>20/30</td>
<td></td>
</tr>
<tr>
<td>61, Female (25) CHC</td>
<td>IFN alpha-2a and ribavirin</td>
<td>Bilateral</td>
<td>8 weeks</td>
<td>20/100 OU</td>
<td>20/25 OU</td>
<td></td>
</tr>
<tr>
<td>71, Male (25) CHC</td>
<td>IFN alpha-2a and ribavirin</td>
<td>Unilateral</td>
<td>7 months</td>
<td>20/100</td>
<td>20/30</td>
<td></td>
</tr>
<tr>
<td>64, Male (24) CHC</td>
<td>IFN alpha and ribavirin</td>
<td>Unilateral</td>
<td>8 months</td>
<td>20/100</td>
<td>Marked improvement</td>
<td></td>
</tr>
<tr>
<td>Unknown (35) Malignant melanoma</td>
<td>IFN alpha</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>40, Male (26) RCC</td>
<td>IFN alpha</td>
<td>Bilateral</td>
<td>3 weeks</td>
<td>20/25</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>51, Male (26) Multiple myeloma</td>
<td>IFN alpha</td>
<td>Bilateral</td>
<td>1 week</td>
<td>20/20 OD; 20/30 OS</td>
<td>20/20 OD; 20/30 OS</td>
<td></td>
</tr>
<tr>
<td>51, Male (28) CHC</td>
<td>IFN alpha-2b and ribavirin</td>
<td>Bilateral</td>
<td>3 months</td>
<td>20/60 OD; 20/80 OS</td>
<td>20/30 OU</td>
<td></td>
</tr>
<tr>
<td>46, Male (30) CHC</td>
<td>IFN alpha-2b and ribavirin</td>
<td>Bilateral</td>
<td>3 weeks</td>
<td>20/400 OD; 20/100 OS</td>
<td>20/80 OU</td>
<td></td>
</tr>
<tr>
<td>51, Male (28) CHC</td>
<td>IFN alpha-2b and ribavirin</td>
<td>Bilateral</td>
<td>3 months</td>
<td>Unknown</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>64, Male (29) CHC</td>
<td>IFN alpha-2b and ribavirin</td>
<td>Bilateral</td>
<td>6 weeks</td>
<td>Unknown</td>
<td>20/20 OD; 20/200 OS (both worsened)</td>
<td></td>
</tr>
<tr>
<td>60, Male (27) Malignant melanoma</td>
<td>IFN alpha-2b</td>
<td>Bilateral</td>
<td>23 weeks</td>
<td>20/120 OD; 20/400 OS</td>
<td>20/120 OD; 20/400 OS</td>
<td></td>
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<tr>
<td>55, Female (39) CHC</td>
<td>IFN alpha-2b and ribavirin</td>
<td>Bilateral</td>
<td>6 months</td>
<td>20/400 OD; 20/80 OS</td>
<td>&lt;20/400 OD; 20/80 OS</td>
<td></td>
</tr>
<tr>
<td>57, Male (32) CHC</td>
<td>IFN alpha-2b and ribavirin</td>
<td>Unilateral</td>
<td>6 months</td>
<td>20/60</td>
<td>20/20</td>
<td></td>
</tr>
<tr>
<td>40, Female (36) CHC</td>
<td>Natural IFN alpha</td>
<td>Unilateral</td>
<td>2 months</td>
<td>20/30</td>
<td>20/20</td>
<td></td>
</tr>
</tbody>
</table>

CHC, chronic hepatitis C; IFN, interferon; NAION, nonarteritic anterior ischemic optic neuropathy; OD, right eye; OS, left eye; OU, both eyes; pegIFN, pegylated interferon; RCC, renal cell carcinoma.
TABLE 2. World Health Organization causality assessment of suspected adverse drug reactions

Certain: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

Possible: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug but that could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Unlikely: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration that makes a causal relationship improbable and in which other drugs, chemicals, or underlying disease provide plausible explanations.

Conditional/Unclassified: A clinical event, including laboratory test abnormality, reported as an adverse reaction about which more data is essential for a proper assessment or the additional data are under examination.

Unassessible/Unclassifiable: A report suggesting an adverse reaction, which cannot be judged because information is insufficient or contradictory and which cannot be supplemented or verified.

NAION occurred within a reasonable time frame following the start of interferon alpha therapy. The cases reviewed could not be clearly linked to the presence of other diseases, underlying risk factors, or other medications.

While improvement in visual acuity was noted following discontinuation of interferon alpha in 9 of the 23 cases reported in the literature, a large, randomized, prospective study of patients with NAION showed that 43% of untreated eyes with vision of 20/64 or worse gained 3 lines or more of vision at a 6-month follow-up (55). It is also unclear whether continuing therapy with interferon alpha results in progressive visual deterioration. The high frequency of bilateral NAION in cases linked to interferon alpha therapy suggests that presentation in one eye may place the fellow eye at risk, especially in patients with small cup-to-disc ratio. Further study is warranted to identify whether discontinuing therapy diminishes the likelihood of NAION in the fellow eye.

In conclusion, treatment with interferon alpha may lead to the development of NAION. Currently, the decision to continue or discontinue interferon alpha in patients presenting with unilateral NAION should be made on a case-by-case basis until proven therapeutic guidelines are established.

REFERENCES


Acute Retrobulbar Optic Neuritis and Macular Detachment Associated With Morning Glory Optic Disc Anomaly

Marjorie A. Murphy, MD, Robert H. Janigian, MD, Theodoros Filippopoulos, MD, Glenn A. Tung, MD, FACR

Abstract: A 31-year-old woman with morning glory optic disc anomaly (MGDA) developed acute retrobulbar optic neuritis and a bullous macular detachment. MRI demonstrated truncation of the perineural space of the affected optic nerve as well as focal optic nerve enhancement. Optical coherence tomography (OCT) showed retinoschisis associated with the macular detachment. The MRI and OCT findings support the vitreous as the source of the subretinal fluid. This is the first reported case of optic neuritis in MGDA.

CASE REPORT

A 31-year-old woman with known MGDA in the left eye presented with a 5-day history of ipsilateral retrobulbar pain exacerbated by eye movement. The pain was not relieved by nonsteroidal anti-inflammatory medications. Her past medical history was notable for hypertension, hypercholesterolemia, and asthma. She denied any current or prior neurologic or constitutional symptoms.

Best-corrected visual acuity was 20/20 in the right eye and hand motions in the left eye, both unchanged from her previously documented baseline. Extraocular motility was full, with a large-angle left exotropia dating back to childhood. A long-standing left afferent pupillary defect was noted. Slit lamp examination of the anterior segment was normal in both eyes. Dilated ophthalmoscopy of the left eye showed a MGDA and a large serous retinal detachment involving the macula, with no visible peripapillary retinal break (Fig. 1). No macular abnormality had been noted in the left eye on a routine examination 1 year earlier. Ophthalmoscopy of the right eye was normal.

MRI of the orbits (Fig. 2) showed focal truncation of the left optic nerve perineural space 4 mm posterior to the sclera and focal enhancement of the corresponding short segment of the retrobulbar left optic nerve. Results of MRI and MRA of the brain were normal.

Optical coherence tomograms (Stratus OCT3) of the macula and optic disc showed conical excavation of the optic disc and a bullous macular detachment (Fig. 3).
Retinoschisis was noted to extend temporally from the optic disc. A definitive connection of the schisis cavity to the subretinal space or the vitreous cavity could not be identified by optical coherence tomography (OCT).

Based on a diagnosis of left retrobulbar optic neuritis, the patient was treated with 1 g intravenous methylprednisolone daily for 3 days, followed by an oral prednisone taper. Periocular pain resolved completely after the 3rd day of treatment. During a follow-up of 1 year, she had no recurrence of symptoms. Visual function remained unchanged and the macular detachment persisted. Eighteen months after presentation, repeat MRI of the brain and orbits showed no change. At 24 months after presentation, the macular detachment had completely resolved.

**DISCUSSION**

This is the first report of MGDA associated with MRI evidence of truncation of the perineural space and retrobulbar optic nerve. We suggest that this observation indicates that the vitreous rather than the cerebrospinal fluid (CSF) is the source of subretinal fluid in our patient’s retinal detachment. With cavitary optic nerve anomalies, dysplastic tissue herniates through a defect in the lamina cribrosa and may extend slightly posteriorly into the subarachnoid space of the distal portion of optic nerve sheath (11). However, it is unlikely that such a potential herniation would extend more than 4 mm to reach beyond the point of truncation of the nerve sheath and into the subarachnoid space. In addition, retinoschisis was noted in our patient, similar to that seen in some patients with optic pit maculopathy, in whom a connection between the schisis cavity and vitreous has been demonstrated (12,13).

Although a retinal break could not be definitively identified by OCT in our patient, the radial lines protocol uses a 30 arc between scans and could have missed a small...

**FIG. 1.** Fundus photograph of the left eye shows a morning glory disc anomaly and associated macular detachment.

**FIG. 2.** Focal absence of the retrobulbar optic perineural space and acute inflammation in the left optic nerve near the globe. Axial T2 (A), FLAIR (B), and postcontrast T1 (C) MRI show focal absence of the left perineural space (arrow, A) corresponding to a short segment of the enhancing retrobulbar left optic nerve (arrow, C). Coronal short-tau inversion recovery images show hyperintense signal within the affected left optic nerve (arrow, D) and around the nerve (arrow, E) compared with the normal signal intensity within and around the unaffected right optic nerve.

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break. Johnson and Johnson (10) have emphasized that the anatomy of cavitary optic disc anomalies varies from one eye to another, with a communication to the vitreous in some eyes and to the subarachnoid space or both spaces in others. Hence, no single unifying mechanism necessarily accounts for the variability and behavior of macular detachments associated with congenital optic disc anomalies.

We believe this to be the first report of acute retrobulbar optic neuritis in association with MGDA. Perkins et al (11) have postulated that undetermined systemic factors may play a role in the development of macular changes in patients with cavitary optic nerve anomalies, noting that one of the patients in their series developed bilateral simultaneous macular detachments associated with bilateral atypical optic nerve colobomas. Systemic as well as local factors may play a role and the inflammatory process in our patient probably contributed to the concurrent development of a macular detachment. This detachment was a new finding from an examination 1 year earlier and had resolved spontaneously within 2 years of follow-up.

This case highlights the fact that patients with profound visual loss from congenital optic disc anomalies may develop superimposed acquired optic neuropathies and emphasizes that those who present with a clinical picture consistent with optic neuritis should undergo neuroimaging.

REFERENCES


FIG. 3. Optical coherence tomography of the left eye. Radial superotemporal cut of the peripapillary region demonstrates retinoschisis and neurosensory retinal detachment.
Cavernous Malformation of the Optic Nerve Mimicking Optic Neuritis

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Abstract: A 30-year-old woman developed acute visual loss and optic disc elevation in the left eye after breast-feeding her second son. The initial diagnosis was optic neuritis. However, MRI showed a lesion in left intraorbital and intracanalicular optic nerve and several cerebral lesions with imaging features of cerebral cavernous malformations (CCMs). Genetic testing was positive for abnormalities known to predispose to CCMs in the patient and her father, who also showed MRI evidence of CCMs. During a 44-month follow-up period in which no intervention took place, the patient’s vision in the affected eye fluctuated but eventually became extinguished. Serial MRIs did not always show lesion changes that explained the visual deterioration. In familial CCM, pregnancy might be a “second hit” to genetically predisposed tissue.

doi: 10.1097/WNO.0b013e3181ceb428
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The distribution of cerebral cavernous malformations (CCMs) follows the volume of the neuraxis, such that 80% are supratentorial, 15% are infratentorial, and 3%–5% are within the spinal cord (1,2). Cranial nerve CCMs constitute a distinctly rare subset, accounting for no more than 1% (3–10). The optic chiasm is most frequently affected (4,7,8) but the prechiasmatic optic nerve extremely rarely (11).

We report a young woman presenting with left optic neuropathy that mimicked optic neuritis, but in whom neuroimaging showed multiple cerebral CCMs with familial features.

CASE REPORT

One week after an 8-month period of breastfeeding her second son, a 30-year-old woman awoke with visual impairment of the left eye. A diagnosis of optic neuritis was made elsewhere. When vision did not improve after 4 retrobulbar corticosteroid injections, she was admitted to our institution for an evaluation.

Our examination disclosed a visual acuity of 20/20 in the right eye and 20/200 in the left eye. There was a left afferent pupillary defect. Ophthalmoscopy showed no abnormalities in the right eye and optic disc edema in the left eye (Fig. 1A). Visual field testing showed no abnormalities in the right eye and blind spot enlargement in the left eye.

Orbital ultrasound showed only elevation of the left optic nerve head. Fluorescein angiography showed no leakage (Fig. 1B). Visual evoked potentials showed no abnormalities upon stimulating the right eye, and increased latency and a reduced P100 amplitude upon stimulating the left eye.

These findings were considered suspicious for left optic neuritis. However, brain and orbit MRI (Fig. 2) showed 2 lesions consistent with CCMs, 1 type III in the left temporal lobe and 1 type II in the right frontal lobe (12), as well as thickening and abnormal signal intensity of the deep intraorbital and intracanalicular portions of the left optic nerve. The optic nerve lesion was considered consistent with a type I CCM. CT did not show calcification in any of the lesions.

Treatment included a 3-day intravenous bolus of prednisone (1 g/day), followed by a month of oral...
administration of prednisolone (50 mg/day), which was then gradually tapered. This treatment resulted in slow improvement in visual acuity of the left eye.

The patient had 2 children, 1 aged 7 years and 1 aged 9 months, as well as a sister aged 25 years, all of whom were apparently healthy. The patient’s father, aged 57 years, had purple-black, round, raised, nontender, angioma-like cutaneous lesions in his right leg noted from birth. With age, these lesions had increased in size and easily bled if traumatized. Biopsy of a right leg lesion showed cavernous hemangioma and MRI (Fig. 3) showed multiple type III and IV CCMs (12) in the brain. Genetic analysis of the proband and her father showed a novel pathogenic G235R mutation in the \textit{KRIT1} gene (13). The genetic test results were negative in the proband’s sister.

A repeat MRI of the proband 4 months later showed reduction in size and signal intensity of the left optic nerve lesion. Four months later, ophthalmologic examination disclosed further improvement of visual acuity in the affected eye to 20/25 with reduction in blind spot enlargement.

However, 5 months later visual acuity in the left eye had regressed to 20/40, and ophthalmoscopy showed increased left optic disc swelling and visual fields showed enlargement of the blind spot. MRI (Fig. 4A) disclosed more left optic nerve thickening and abnormal signal intensity.

Oral administration of acetazolamide (250 mg/day) and some days later oral administration of prednisolone (50 mg/day) for 1 month with subsequent tapering resulted in complete visual recovery. Yet 5 months later, the visual acuity of the left eye regressed again, this time to finger counting. MRI (Fig. 4B) did not show acute or subacute changes. Treatment included a 3-day intravenous bolus of prednisone (1 g/day) and oral administration of acetazolamide (250 mg/day), followed by oral administration of 50 mg/day prednisolone for 1 month with subsequent tapering. However, 1 month after treatment had been started, visual acuity had declined to hand movements in the left eye.

MRI (Fig. 4C) now showed an increase in the size and signal of the intraorbital left optic nerve CCM. Seven months later, visual acuity was no light perception in the left eye. At this stage, MRI showed regression of the optic nerve CCM. Eight and 20 months later, MRIs were unchanged.

**DISCUSSION**

We have described a patient who had sudden visual loss in 1 eye with optic disc elevation but no fluorescein leakage that mimicked optic neuritis but proved to be a presumed CCM in conjunction with multiple cerebral CCMs. No intervention occurred, and over several months of fluctuations, visual function was eventually extinguished in that eye.

For CCMs in any location in the neuraxis, MRI is the method of choice for diagnosis, classification, and follow-up (1,2,12). T2* MRI provides the definitive evaluation of the total number of CCMs because of the susceptibility artifacts from microscopic deposits of hemosiderin in chronic phases of hemorrhage. On the other hand, the combination of T1 and T2 images is best to show the acute and subacute hemorrhages. A major limitation of T2* images is the severe signal loss induced by macroscopic field inhomogeneity and diamagnetic susceptibility artifacts at interfaces, which are
Type I CCMs appear homogeneously hyperintense on T1 images due to methemoglobin predominance in subacute hemorrhage. Type II CCMs are heterogeneous on both T1 and T2 sequences, showing a reticulated mixed signal core ("popcorn"). Type III CCMs are hypointense to isointense on T1 images, hypointense on T2 images, and markedly hypointense on T2* images due to hemosiderin predominance. Type IV CCMs show tiny, punctate foci that are hypointense on T1 and T2 images, often multiple, and best seen on T2* images (2,12). Type IV CCMs rarely enhance, simulating capillary telangiectasias (14,15). None of these 4 MRI appearances is immune from changes into another MRI appearance, and the evolution is not predictable on the basis of the original morphology (1,15,16).

Several authors have noted that patients with type I and type II CCMs are more commonly symptomatic compared with patients who have type III and type IV CCMs (12,16–18). This seems consistent with the history of our patient, but other authors did not find any significant correlation between symptoms and serial MRI changes (15). Perilesional edema and mass effect may correlate with the patient’s clinical manifestations.

Although our patient was originally believed to have optic neuritis, the MRI signal characteristics of the lesion
Brain MRI follow-up in the proband. T2* (gradient echo) axial images show swelling and high signal intensity of the left optic nerve (arrows) 9 months after diagnosis (A), thinning and normal signal intensity 15 months after diagnosis (B), and relapse of swelling and high signal intensity 16 months after diagnosis (C). Open arrowheads indicate a cavernous malformation in the left temporal lobe.

were not consistent with that diagnosis. In optic neuritis, the optic nerve shows abnormal signal intensity including low or normal signal intensity on T1 images, high signal intensity on T2 images, and enhancement (19,20). The optic nerve is swollen in the acute phase and may undergo atrophy in the chronic phase (21). In the acute phase, optic neuritis may also present with optic nerve sheath dilatation, probably due to interruption of the communication between the subarachnoid space of the diseased optic nerve and the chiasmal cistern. Optic nerve sheath enhancement suggests meningeal inflammation, as observed in pathologic studies (22).

The MRI findings were also not consistent with a tumor of the optic nerve or optic nerve sheath (23–28), including hemangioblastoma, a benign vascular tumor commonly associated with von Hippel-Lindau disease. Most hemangioblastomas that occur within the orbit are located in the retina, although locations within the optic nerve have been reported. Hemangioblastomas generally show an enhancing portion (23–26).

Cerebral CCMs, which account for 5%–20% of all cerebral vascular malformations, are reported in 0.3% of large autopsy studies, and 0.4%–0.9% of large prospective cohort studies of the general population. Most (50%–80%) CCMs are apparently sporadic. A single CCM may be found in roughly 70% of patients with sporadic CCMs and in 8%–19% of patients with familial disease. Multiple CCMs, indicative of familial forms (1,2,12,13,18,29), are genetically heterogeneous, exhibiting an autosomal dominant inheritance with different preliminary estimates of disease penetrance at 3 loci: KIRTI/CCM1, CCM2, and PDCD10/CCM3, mapped to 7q, 7p, and 3q, respectively. These loci account for approximately 40%, 20%, and 40% of non-Hispanic familial cases, respectively.

Familial CCMs have been shown to have a 0.2%–0.4% incidence per patient per year of de novo lesion formation (1,2,12,18). For this phenomenon, 2 possible developmental mechanisms have been postulated: a Knudson 2-hit mechanism and a haploinsufficiency mode (30–33). De novo formation has been associated with previous irradiation, viruses, hormonal influences in pregnancy, endothelial proliferation, and angiogenesis (2,34–36). Notably, CCMs have the capacity for endothelial proliferation and neoangiogenesis, which may also explain the development of new CCMs along a biopsy tract (35). A small amount of cavernous tissue transplanted to any point along the biopsy tract may induce the transformation of normal capillaries or the growth of new, fragile vessels or recanalization by nearby parenchymal vessels (36).

In the patient reported here, the visual loss started 8 days after the end of breast-feeding. Some authors suggested that pregnancy is a risk factor for growth of intraorbital tumors (37), hemorrhage from cerebral vascular malformations (38) or CCMs (17,39–43), or onset of CCM-related seizures (44), resulting in an aggressive clinical course, especially in the first trimester of pregnancy. However, another series (45) did not find an increase in the risk of CCM hemorrhage in pregnant women, and the paucity of cases in the literature would argue against this hypothesis. Although the biologic effects on CCMs of hormonal and hemodynamic alterations experienced during pregnancy are unknown, in the patient reported here they might have represented a “second hit” to genetically predisposed tissue.

Symptoms of CCMs are thought to result from recurrent episodes of hemorrhage and CCM growth. However, these changes need not cause clinical manifestations. Hemorrhage is characteristically confined within the lesion and may not result in neurologic deficits unless it creates a mass effect. Asymptomatic episodes of small hemorrhage may thus occur (46). On the other hand, clinical deterioration may also occur without any evidence of lesion change on MRI (47). This phenomenon seems consistent with the fact that in anterior visual pathway CCMs, the rise and fall of visual acuity is not necessarily associated with neuroimaging documentation of recurrent tissue hemorrhage (48), as exemplified by our patient.

Surgery may be indicated in symptomatic and accessible CCMs in noneloquent parenchyma. Symptomatic patients with inaccessible lesions are usually observed, despite the often poor natural history. The role of stereotactic radiosurgery in the treatment of CCMs is still debated (2,4). In our patient, the involvement of the proximal intracranial and intracanalaricular segments of the optic nerve precluded surgery or irradiation.
REFERENCES


Spontaneous Postpartum Resolution of Vision Loss Caused by a Progesterone Receptor–Positive Tuberculum Sellae Meningioma

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Abstract: A 27-year-old pregnant woman reported progressive loss of vision. Brain MRI disclosed an intracranial mass compressing the optic nerves and chiasm with imaging features suggestive of meningioma. Because delivery was imminent, surgical removal was deferred. Within a few days after delivery, the patient noted improvement in vision. Subsequent neuro-ophthalmological evaluations documented almost complete visual recovery within 2 months postpartum. The mass was removed surgically at 10 months postpartum. It was a grade I meningioma with progesterone cell surface receptors. The patient’s visual function has remained stable during a follow-up of 14 months. This is the first reported case with full visual function and MRI documentation of spontaneous postpartum visual recovery in a progesterone receptor–positive meningioma compressing the anterior visual pathway.

CASE REPORT

A 27-year-old woman in her 26th week of pregnancy presented with a 2-week history of vision loss in the right eye. She also complained of headaches with nausea and vomiting for 4 months. Medical history included migraine and spastic diplegic cerebral palsy. She had had 2 preterm deliveries at 28 and 29 weeks.

Visual acuity was count fingers at 3 feet in the right eye and 20/15 in the left eye. Color vision by Ishihara plates was 1/11 in the right eye and 11/11 in the left eye. Pupils measured 7 mm bilaterally in dim illumination, with trace reaction to light in the right eye and brisk reaction in the left eye and a 1.5 log unit afferent pupillary defect in the right eye. Ophthalmoscopy was normal. Automated visual fields showed dense temporal loss in the right eye and a mild inferotemporal defect in the left eye (Fig. 1A). Brain MRI without contrast showed a suprasellar mass measuring 11 × 14 mm that was compressing the optic chiasm, most suspicious for meningioma.

At 29 weeks of pregnancy, she was complaining of contractions and a further decline in vision. Visual acuity had decreased to hand motion in the right eye and 20/30 in the left eye. The afferent pupillary defect had decreased to 0.9 log units, perhaps owing to increasing dysfunction of the left optic nerve. Ophthalmoscopy remained normal. Visual fields (Fig. 1B) showed worsening defects. Repeat
Magnetic resonance imaging (MRI) with contrast (Fig. 2A) was consistent with mild tumor enlargement since the previous study. Because of imminent delivery, surgery was postponed and instead she underwent uncomplicated cesarean section at 30 weeks of pregnancy.

Within a few days after delivery, she noted improvement in her vision. At 1 month after delivery, visual acuity was 20/40 in the right eye and 20/20 in the left eye. Color vision had improved to 11/11 in both eyes. The right afferent pupillary defect had decreased to 0.6 log units. Visual fields were markedly improved.

At the 8-week postpartum visit, left visual acuity had further improved to 20/25. The right afferent pupillary defect now measured only 0.3 log units. Visual fields were nearly normal (Fig. 1C).

At 24 weeks postpartum, the MRI tumor dimensions in the coronal plane had slightly regressed (Fig. 2B). Visual function remained stable.

At 40 weeks postpartum, the tumor was electively removed. It was a World Health Organization grade I meningioma. Tumor cells were strongly positive for progesterone receptor and negative for estrogen receptor. Neuro-ophthalmologic follow-up has documented stable visual function for 14 months since her recovery.

**DISCUSSION**

This is the first reported case with visual field and neuro-imaging documentation of spontaneous postpartum resolution of visual loss due to an anterior visual pathway compressive intracranial meningioma with progesterone cell surface receptors. The meningioma probably displayed an accelerated growth pattern during the second half of pregnancy due to increasing levels of progesterone.

Most cases involving hormonally responsive intracranial meningiomas detected during pregnancy have been urgently removed surgically, either during the pregnancy or within a few days after delivery (4–8). Adverse events can

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**FIG. 1.** Automated 30-2 visual fields at 26 weeks of pregnancy (**A**), 29 weeks of pregnancy (**B**), and 8 weeks after delivery (**C**).

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**FIG. 2.** **A.** Coronal postcontrast T1 MRI at 29 weeks of pregnancy reveals an enhancing mass with features of a tuberculum sellae meningioma. **B.** Coronal postcontrast T1 MRI at 24 weeks after delivery reveals only slight reduction in tumor size.
accompany neurosurgery on gravid patients. Among 12 gravid patients with visual loss caused by compressive intracranial meningiomas who have undergone craniotomy, the fetus died in 2 (4,6–8).

The phenomenon of spontaneous visual improvement after delivery in patients with anterior visual pathway compressive meningiomas has been previously reported but with less documentation. Kanaan et al (7) mentioned 2 patients with compressive meningiomas whose vision improved spontaneously postpartum but did not report visual acuity, visual field, or MRI changes. Johnson et al (8) also reported one patient whose vision spontaneously improved postpartum. Optic neuritis had been the initial clinical diagnosis, but a postpartum brain MRI showed a tuberculum sellae meningioma.

We theorize that our patient improved postpartum because progesterone levels decreased with delivery of the placenta. Without this trophic factor present, the meningioma regressed mildly in size, and the optic nerves were decompressed. Prior to surgery, the patient was advised not to breast-feed or become pregnant because the increased progesterone levels could result in a return of her vision loss. The pituitary also enlarges during late pregnancy and thus can further elevate a meningioma to compress the optic nerve/chiasm (5). It is important to note that our patient did not observe visual improvement immediately after delivery but rather a few days later.

Because the patient became asymptomatic and repeat automated visual fields showed resolution of visual field loss, no immediate neurosurgical intervention was indicated. Urgent surgery was thus avoided at a critical time when mother-baby bonding normally occurs.

REFERENCES
Ectopic Pituitary Adenoma in the Spheno-Orbital Region

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Abstract: Ectopic pituitary adenomas (EPAs) are rare tumors that most often occur in the sphenoid sinus or suprasellar region. We describe a 66-year-old man who presented with unilateral proptosis and an ipsilateral abduction deficit caused by an EPA in the spheno-orbital region. The tumor was completely excised with elimination of proptosis and restoration of full ocular ductions. There were no complications. Diagnosis of a hormonally inactive EPA was reached on the basis of immunohistochemical studies of the operative specimen. This is the first documented case of an EPA in this location. It may have originated from Rathke pouch remnant cells in the lateral wall of the sphenoid sinus.

doi: 10.1097/WNO.0b013e3181c5d1a2
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First described by Erdheim (1) in 1909 as “a growth hormone-secreting tumor in the sphenoid sinus,” ectopic pituitary adenoma (EPA) is rarely encountered. Although it originates from the adenohypophysis, it is separated from the pituitary gland, being most often detected in the sphenoid sinus, suprasellar region, clivus, and cavernous sinus (2). Its occurrence in the spheno-orbital region has not been reported previously. We present such a case.

CASE REPORT

A 66-year-old man presented with a 2-month history of right proptosis and double vision. Our examination disclosed that visual acuity was 20/20 in both eyes and visual fields were intact. A bulge of his right temporal region was evident, and there was mild proptosis of the right eye, with a Hertel exophthalmometry (TMI-90, T.M.I. Company, Ltd., Saitama, Japan) reading of 22 mm on the right and 14 mm on the left. There was a complete right abduction deficit. No clinical signs of Cushing disease, acromegaly, or hyperthyroidism were detected. Routine biochemical investigations were within normal limits.

Brain MRI showed an irregular solid enhancing mass, approximately 3.5 cm × 4 cm × 4 cm in size, located at the junction of the right orbital cavity and middle cranial fossa (Fig. 1A–B). The pituitary gland, residing within a normalized sella turcica, was unaffected (Fig. 1C, large arrow). The tumor was slightly hyperdense on precontrast CT (Fig. 1D), and bone windowing revealed that the right lateral orbital wall and greater sphenoid wing were eroded by the tumor (Fig. 1E). The lesion was believed to be a meningioma or metastatic tumor.

Right frontotemporal craniotomy revealed a soft gray-white tumor with a rich blood supply at the junction of the temporal polar epidural space and the orbital cavity. The lesion extended exteriorly through the eroded great sphenoid wing into the temporalis muscle and anteriorly through the expanded superior orbital fissure into the orbit with anterolateral displacement of the intact periorbita. Medially the tumor encroached on the lateral wall of the sphenoid sinus and a fraction of the tumor seemed to protrude into the sinus.

After resection of the intraorbital tumor, the orbital contents were covered with a gelatin sponge and fibrin glue, providing further support to the orbital cone. No extension of the tumor into the subdural space was detected, but the fact that the tumor had a poor plane of cleavage from the temporal dura in some places demonstrated its invasiveness. The tumor was totally excised with the involved dura. Frozen section suggested pituitary adenoma. Postoperative CT revealed apparent total excision of the tumor (Fig 1F).

On sections stained with hematoxylin and eosin, the tumor was composed of small uniform chromophobic cells arranged in a sinusoidal pattern with cellular atypia (Fig. 2A). On histochemical staining, these cells showed negative reactivity to growth hormone (Fig. 2B) or other anterior pituitary hormones.

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pituitary hormones, but positive reactivity to neuron-specific enolase (not shown). This is the characteristic staining pattern of a hormonally inactive pituitary adenoma.

The patient’s postoperative course was uneventful. Serum levels of anterior pituitary hormones were normal. No new neurologic deficits in addition to pulsatile proptosis were observed. Three months after surgery, the proptosis was gone, with Hertel readings of 15 mm on both sides. Eye movements were normal, and diplopia was no longer present.

DISCUSSION

Most sphenoid-orbital tumors are meningiomas, fibrous dysplasias, plexiform neurofibromas, or metastatic tumors. Mesenchymal chondrosarcoma, angiosarcoma, and encephalocele are other unusual sphenoid-orbital lesions (3–5), but as far as we are aware, EPA in the sphenoid-orbital region has never been reported.

The putative origin of infrasellar EPAs differs from that of suprasellar EPAs, which are supposed to come from ectopic non-neoplastic pituitary cells in the leptomeninges of the suprasellar peri-infundibular region (6). Remnants of the developing tissue are often deposited along the route of upward migration of Rathke’s pouch from the third to seventh week of gestation (7). Conceivably, these ectopic remnant cells around the sella and nasopharynx can be stimulated by several genetic and environmental factors to eventually develop into pituitary tumors (8).

As for the present case, we hypothesize that the remnant cells of Rathke’s pouch may have migrated into the lateral wall of the sphenoid sinus and undergone a neoplastic proliferation in this location. With bone eroded, the lesion probably broke through the medial margin of the superior orbital fissure to occupy the medial part of the fissure. It probably grew in 2 directions: posterolaterally toward the temporal polar epidural space and anterolaterally to destroy the thin edge of the greater sphenoid wing and invade the orbit.

The preoperative diagnosis of hormonally inactive EPAs is quite difficult from that of hormonally active EPAs, because patients with the former do not show any endocrine symptoms and signs. The main clinical manifestations are headache or sinus fullness, nasal congestion, and cranial nerve paralysis caused by the tumor invasion of the sphenoid sinus, nasal cavity, and cavernous sinus, respectively.

FIG. 1. A. Precontrast T1 axial MRI shows an extraaxial isointense solid mass at the junction of the right orbital cavity and middle cranial fossa. B. Postcontrast T1 axial MRI shows dense enhancement of the tumor. C. Postcontrast sagittal MRI shows a normal pituitary gland (arrow). D. Precontrast axial CT shows that the tumor is slightly hyperdense. E. Precontrast axial CT at bone window setting shows erosion of the right lateral orbital wall and the greater sphenoid wing by the tumor (arrows). F. Postoperative precontrast CT shows complete excision of the tumor.

FIG. 2. Histopathologic analysis of the tumor (×400). A. Hematoxylin and eosin stain shows that the tumor is composed of small uniform chromophobic cells arranged in a sinusoidal pattern with cellular atypia. B. Growth hormone stain shows no immunoreactivity.
(9–11). Visual disturbances result from impingement on the optic nerves or chiasm by suprasellar EPAs (12,13). However, unilateral exophthalmos is extremely rare, with only 1 case described previously (14). In that case, a pro-lactin-secreting EPA was found in the sphenoid sinus with extension to the clivus and medial aspect of the middle cranial fossa. The proptosis, which was attributed to occlusion of opthalmic veins, disappeared 1 year after surgery. In our patient, the proptosis was most likely caused by direct compression of the orbital contents by the tumor and was understandably relieved quickly after total removal of the tumor.

On CT, EPAs appear relatively isodense or slightly hypodense with distinct margins. MRI of this lesion shows isointensity on T1 images, slight hyperintensity on T2 images, and uniform enhancement, a pattern similar to that seen in sphenoid orbital meningiomas. Differentiating between EPAs and the more common meningiomas is important because patients with meningiomas are more likely to need invasive surgical techniques, have more frequent surgical complications, and have a less favorable clinical outcome (15). Features that favor the diagnosis of EPA over meningioma are epidual location of the tumor, surrounding bone erosion, and absence of marked hyperostosis and carpet-like dural involvement. Other possible diagnoses after imaging studies in the sphenoid-orbital region include fibrous dysplasia, peripheral nerve sheath tumor, and metastatic tumor. In this location, a neuroendocrine carcinoma or an undifferentiated carcinoma are additional diagnostic considerations. A correct distinction is important because EPAs have a much more favorable prognosis and a low metastatic potential.

The clues to diagnosis of an EPA are an endocrine growth pattern, a very low mitotic count, and evidence of neuroendocrine markers and pituitary hormones. Hormonally inactive EPAs are usually cellular and composed of the chromophobic, small- to medium-sized monomorphic cells arranged in a sinusoidal pattern. Some pseudorosettes may be present. Mitotic cells are rare in the presence of nuclear atypia. The usual immunohistochemical pattern shows negativity for all anterior pituitary hormones and positivity for neuron-specific enolase (16), features seen in our patients.

Early diagnosis and treatment of patients with EPAs could potentially lead to improved outcomes. Complete surgical removal should be attempted. If this cannot be achieved, postoperative radiotherapy is recommended (17). Our experience, limited as it is, indicates that complete surgical removal of this sphenoid-orbital lesion is quite safe and effective. However, in 2002, Hosaka et al (18) reported a patient with invasive EPA with malignant transformation after repeated relapses. In that patient, an EPA-producing folllicle-stimulating hormone was found in the nasal cavity and extended to the frontal cranial fossa. Despite repeated surgical resections of the tumor, it recurred 3 times in 2 years. The patient died of the tumor 10 months after the last resection with multiple metastases in the subarachnoid space and brain parenchyma. The biologic behavior of EPAs will remain unclear until a longer follow-up in a larger patient cohort is available. Meanwhile, patients with these lesions, especially the invasive ones, should be followed closely.

REFERENCES
Stereotactic Radiosurgery in the Treatment of a Dural Carotid-Cavernous Fistula

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Abstract: Because of the success of stereotactic radiosurgery (SRS) in the treatment of cerebral arteriovenous malformations (AVMs), SRS is being applied to the treatment of carotid-cavernous dural arteriovenous fistulas (CCDAVFs) when these lesions are not accessible endovascularly. We report a patient with a CCDAVF that could not be accessed endovascularly on 2 attempts, whose fistula was successfully closed with SRS, a less invasive modality than endovascular embolization. Further experience with SRS in this role will be necessary to determine its utility.

doi: 10.1097/WNO.0b013e3181ceb3e3
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Carotid-cavernous dural arteriovenous fistulas (CCDAVFs) are abnormal vascular communications between branches of the carotid artery system and the cavernous sinus (1). The natural course of CCDAVFs ranges from spontaneous thrombosis to fatal intracranial hemorrhage (1). Visual deterioration, diplopia, hemorrhage, headache, orbital symptoms such as intolerable bruit, and significant proptosis are indications for treatment, usually by endovascular embolization (2,3). However, a major disadvantage of endovascular embolization is difficulty accessing the vascular lesion because of the small size and orientation of particular arterial branches relative to the internal carotid artery (4). Because of the success of stereotactic radiosurgery (SRS) in the treatment of cerebral arteriovenous malformations (AVMs) (5–7), SRS is now being applied to the treatment of CCDAVFs when these lesions are not accessible endovascularly (8–12).
In this report, we describe the use of SRS to treat a CCDAVF recalcitrant to conventional endovascular embolization techniques.

**CASE REPORT**

A 54-year-old man with no significant past medical history presented with periorcular swelling and a redness of the left eye for several weeks. MRI demonstrated enlargement of the left superior ophthalmic vein.

Visual acuity was 20/20 in both eyes. Pupillary reflexes were normal. The left eye displayed 8 mm of proptosis (Fig. 1, top). An orbital bruit could not be auscultated. Eye movements were normal. Slit lamp examination revealed corkscrew configuration of the conjunctival vessels of the left eye. Intraocular pressures were 19 mmHg in the right eye and 26 mmHg in the left eye. Dilated fundus examination was normal in the right eye, and there was engorgement of the retinal veins and scattered retinal hemorrhages in the left eye (Fig. 1, bottom).

![FIG. 2. Before treatment, time-resolved angiography with stochastic trajectories MRA shows early filling of the left superior ophthalmic vein (red arrow) and the left facial vein (blue arrow) due to the carotid-cavernous fistula. Note the later filling of the remaining venous structures, such as the superior sagittal sinus (green arrow). Because of a technical phenomenon (the “wraparound” effect), a portion of the patient’s common carotid artery appears in the superior portion of the images (yellow arrow) and is not a true representation of the patient’s anatomy.](image-url)

![FIG. 3. Before treatment, a left internal carotid angiogram (A, early arterial phase; B, midarterial phase; C, late arterial phase) shows premature filling of the superior ophthalmic vein (arrow).](image-url)
Brain MRA using time-resolved angiography with stochastic trajectories (TWIST) protocol demonstrated abnormal early filling of the left superior ophthalmic vein and facial vein consistent with a CCDAVF (Fig. 2). Catheter-based angiography confirmed the MRA findings (Fig. 3).

Endovascular embolization via a transfemoral arterial approach was unsuccessful because of an anomalous vascular anatomy preventing optimum migration of the catheter to the site of the fistula. Several weeks later, a second endovascular embolization by transvenous and superior ophthalmic vein approaches was again unsuccessful at approaching the fistula.

SRS was performed on the lesion with a 7-arc plan, using the mini multileaf collimator generated by Radionics XKnife RT software (version 3.0.1; Integra Radionics, Burlington, MA). Treatment with 1,400 cGy was prescribed to the 96% isodose line (Fig. 4), yielding a tissue-to-volume ratio (TVR) of 2.5. The patient underwent treatment on a Varian 2100EX linear accelerator (Varian Medical Systems, Palo Alto, CA).

Within 3 months of treatment, the patient had remarkable improvement in intraocular pressure, proptosis, conjunctival injection (Fig. 5, top), and venous stasis retinopathy (Fig. 5, bottom). Follow-up MRA did not show...
any enhancement of venous structures, indicating closure of the fistula (Fig. 6).

**DISCUSSION**

Our patient underwent successful SRS treatment of an endovascularly inaccessible CCDAVF.

SRS has been studied sparingly in this capacity (9,10,13–15). It involves inducing selective vascular injury, resulting in obliteration of the vascular lumen (9). A therapeutic dose of radiation (between 20 and 50 Gy) leads to a variety of vascular changes, including perivascular/subendothelial edema, fissuring of the vessel wall, spot hemorrhages, thrombi, degeneration and necrosis of endothelial cells, increased interstitial colloids, and increased fibroblastic activity (9). Based on 7 published case series, the treatment of CCDAVF with SRS has shown a complete obliteration rate of these lesions that ranges from 50% to 100% (Table 1) (8–13,16). The authors cited the advantages of using SRS when the vascular lesion was inaccessible endovascularly or when endovascular treatment would have resulted in a high risk of complications (8–12).

A staged, multimodal approach combining endovascular embolization with SRS (12) offers a method of providing the immediate yet sometimes temporary resolving effects of endovascular embolization and the delayed yet permanent benefits of SRS.

Most published studies have focused on SRS in the treatment of brain AVMs, which involve the pial vessels (17,18). Unlike brain AVMs, CCDAVFs are extradural and do not have a nidus of hybrid abnormal vessels at their center (1,19). Whether these differences will affect the success of SRS in CCDAVF is unknown.

An advantage of SRS over endovascular embolization is its less invasive nature (9). A potential drawback is the latency period of obliteration after treatment, during which patients are at risk for cerebral hemorrhage (20). Fortunately, compared with AVMs, CCDAVFs seem to react more promptly to radiosurgery, with the earliest closure observed at 6 months (9). Fractionated radiotherapy may not be as effective (9).

An interesting aspect in the management of our patient was the use of TWIST MRA, which showed remarkable visualization of the fistula comparable to the current gold standard.

**FIG. 6.** Three months after stereotactic radiosurgery treatment, time-resolved angiography with stochastic trajectories MRA no longer shows retrograde venous filling. Filling of the facial vein (white arrow) is concurrent with filling of other venous structures, as is the filling of the superior ophthalmic vein (black arrow).
<table>
<thead>
<tr>
<th>Study</th>
<th>Age Range of Patients (years)</th>
<th>No. Patients/Sex</th>
<th>CCDAVF Type*</th>
<th>Treatment Before SRS</th>
<th>Radiation Dose (Gy)</th>
<th>Complications</th>
<th>Follow-up Period</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soderman et al. 2006 (8)</td>
<td>Not reported</td>
<td>49 patients with 52 cases, gender not reported</td>
<td>16 cases type I (Borden) or types I and IIA (Cognard)</td>
<td>9 treated with embolization or surgery prior to radiation</td>
<td>GKR; average 22</td>
<td>1. One patient: 6th cranial nerve palsy that resolved 2. One patient: late radiation reaction with hemorrhage occurring approximately 10 years after radiosurgery 3. One patient: posterior fossa bleed 2 months after radiosurgery 4. One patient: asymptomatic occipital hemorrhage approximately 6 months postradiosurgery</td>
<td>2 years</td>
<td>41 cases with 2-year follow-up angiography: 28 CO, 10 PO, 3 no change</td>
</tr>
<tr>
<td>Koebbe et al. 2005 (10)</td>
<td>50–89</td>
<td>18 (9 F, 9 M)</td>
<td>Barrow B, C, and D</td>
<td>9 embolization</td>
<td>GKR: mean margin radiosurgery dose was 20</td>
<td>1. One patient: temporary hemiparesis after GKR 2. Two patients: permanent neurological deficits resulting from embolization prior to radiosurgery</td>
<td>2–116 months (mean 43 months)</td>
<td>9 CO, 5 “smaller on MRI”, 1 died before follow-up, 1 no change but symptoms improved, 2 no imaging</td>
</tr>
<tr>
<td>Onizuka et al. 2003 (11)</td>
<td>67–79</td>
<td>4 (all F)</td>
<td>Barrow 3 D, and 1 D→B</td>
<td>1 embolization</td>
<td>GKR: 26–30 (max dose)</td>
<td>No significant side effects reported</td>
<td>14–32 months (mean 24 months)</td>
<td>4 CO</td>
</tr>
<tr>
<td>Study</td>
<td>Age Range of Patients (years)</td>
<td>No. Patients/Sex</td>
<td>CCDAVF Type*</td>
<td>Treatment Before SRS</td>
<td>Radiation Dose (Gy)</td>
<td>Complications</td>
<td>Follow-up Period</td>
<td>Outcome</td>
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<tr>
<td>Guo et al. 1998 (9) (Taiwan)</td>
<td>29–75</td>
<td>18 (12 F, 6 M)</td>
<td>Barrow B, C, and D</td>
<td>None</td>
<td>GKR: 22–38 (mean 28)</td>
<td>No complications reported</td>
<td>6–27 months (median 12 months)</td>
<td>12 CO, 3 PO, 1 died of other causes, 2 no data</td>
</tr>
<tr>
<td>Barcia-Salorio et al. 1994 (13) (Spain)</td>
<td>Not reported</td>
<td>25, gender not reported</td>
<td>Barrow B (11), C (4), D (7), T (3, traumatic, high flow)</td>
<td>None</td>
<td>Conventional radiation therapy: 20–40</td>
<td>Not reported</td>
<td>15 months–14 years (mean 49.76 months)</td>
<td>100% CO of type B, 75% CO of type C, 85.7% CO of type D, 33% CO of type T*</td>
</tr>
<tr>
<td>Barcia-Salorio et al. 1991 (15) (Spain)</td>
<td>Not reported</td>
<td>20, gender not reported</td>
<td>Low flow CCF</td>
<td>None</td>
<td>Conventional radiation therapy: 36–40</td>
<td>Not reported</td>
<td>Not reported</td>
<td>‘90% cure’</td>
</tr>
</tbody>
</table>

CCDAVF, carotid cavernous dural arteriovenous fistulas; CCF, carotid cavernous fistula; CO, complete obliteration; F, female; GKR, gamma knife radiosurgery; Gy, gray; M, male; PO, partial obliteration; SRS, stereotactic radiosurgery; "T, traumatic, high-flow fistulae with flow reduction after internal carotid trapping (type of CCDAVF based on author’s classification).
standard catheter-based angiography (21). Recent advances in dynamic magnetic resonance instrumentation, including an improved signal-to-noise ratio due to the availability of higher field strength magnets and improved temporal resolution due to the development of parallel imaging techniques, have made TWIST an attractive option. However, it lacks the spatial resolution to demonstrate small feeding vessels of CCDAVF's, such as the inferolateral arterial trunk, the meningohypophyseal arterial trunk, and the artery of the foramen rotundum. Detailed information pertaining to the anatomy of the venous system is also not demonstrated owing to limited spatial resolution. Furthermore, dynamic MRA does not allow the demonstration of structural changes and detailed morphology of the cavernous sinuses. There is no large study comparing dynamic MRA with conventional catheter angiography in demonstrating retrograde cortical reflux, one of the most pressing indications for treatment of carotid-cavernous fistulas.

ACKNOWLEDGMENTS

Permission was obtained from the patient to publish his image. The authors thank Neil Miller MD (Johns Hopkins University, Baltimore, Maryland) for his assistance and expertise in the treatment of our patient.

REFERENCES

Midbrain Cleft as a Cause of Chronic Internuclear Ophthalmoplegia, Progressive Ataxia, and Facial Weakness

Omar Ahmad, FRACP, Stephen Reddel, FRACP, Christian J. Lueck, PhD, FRCP, FRACP

Abstract: A 44-year-old man with progressive ataxia, facial weakness, bilateral adduction deficits, and abducting nystagmus was initially misdiagnosed and treated for multiple sclerosis because a midbrain anatomic cleft had been overlooked on brain MRI. Six cases of “midbrain (or mesencephalic) cleft” or “keyhole aqueduct syndrome” have been previously reported. This developmental anatomic abnormality always manifests bilateral internuclear ophthalmoplegia (INO), often together with ataxia, which may be progressive and debilitating. Because the INO is chronic, patients may have no visual symptoms. The cause of a midbrain cleft is uncertain, but it may be the midbrain version of a syrinx. There is no known effective treatment.

doi: 10.1097/WNO.0b013e3181da2ceb
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Midbrain (or mesencephalic) clefts are cerebrospinal fluid (CSF)–containing slit-like ventral extensions of the cerebral aqueduct lined by a combination of ependymal and neuroglial tissues. Although rostral extension is most often seen, complete bisection of the midbrain is also possible. The cause is unknown, and there is currently no useful treatment. These clefts have been reported to cause ataxia and bilateral internuclear ophthalmoplegia (INO), together with other ocular motor abnormalities, usually giving rise to very long-standing symptomatology (1–4). Previous authors (1–4) have shown that although the most prominent findings relate to midbrain involvement, more widespread brainstem and cerebellar manifestations can also be seen, often leading to misdiagnosis.

We present a case of a midbrain cleft, which differs from previous reports by presenting mostly as an ataxic syndrome with an incidental finding of INO without visual symptoms.

CASE REPORT

A 44-year-old man was referred to our department with progressive ataxia and facial weakness. Bilateral INO had also been noted, but he had no visual complaints.

The patient had first come to medical attention 7 years earlier when a neurologist described bilateral INO in assessing the patient after he had fainted following a routine inguinal hernia repair. The patient had no diplopia or other visual symptoms. The patient manifested mild ataxia. He acknowledged then that he had been uncoordinated for at least 10 years in doing sporting activities. He was given a tentative diagnosis of multiple sclerosis (MS), although brain MRI, lumbar puncture, and visual evoked responses were reported as normal. He was treated with 2 courses of intravenous methylprednisolone without symptomatic improvement.

Over the 2 years preceding our examination, he had begun to notice a drunken gait and had experienced several falls. He believed that his arms were better coordinated than his legs. During the year prior to consulting us, he had also developed bilateral facial weakness with difficulty whistling, blowing out his cheeks, and closing his right eye.

There was no history of excessive alcohol intake. He had been adopted as a child and had no knowledge of his family history.

Visual acuity, visual fields, pupillary responses, and ophthalmoscopy were normal. There was an abduction deficit in both eyes, nystagmus of the abducting eyes, and upbeat nystagmus on upgaze. There was a mild exotropia in primary position. Convergence was retained, and his eye...
movements were otherwise normal. Mild bilateral facial weakness was also apparent, with incomplete closure of the right eye. The remainder of the neurological examination revealed normal strength in all limbs, normal sensation, symmetrically depressed reflexes, and flexor plantar responses. There was no ataxia in the upper limbs, but he had a wide-based casual gait and an inability to perform tandem gait. No oculocutaneous features of neurofibromatosis were present.

Negative or normal laboratory studies included vitamin B₁₂; vitamin E; phytanic acid and hexosaminidase levels; serum angiotensin-converting enzyme; autoantibody screen; antineuronal antibodies; anti-GM1 antibodies; and genetic studies for spinocerebellar ataxias types 1, 2, 3, and 6.

A repeat brain MRI revealed a midline cleft at the level of the midbrain (Figs. 1, 2). The cleft was in continuity with the fourth ventricle, which was somewhat expanded and showed a rectangular appearance. The cerebral hemispheres, cerebellum, cisterns, and foramen magnum were unremarkable, but there was a small syrinx in the cervical spinal cord (Fig. 3). High-resolution 3T images of the aqueduct and fourth ventricle did not reveal any other anatomic abnormalities. Review of the previous MRI indicated that the cleft had been present but overlooked. The cleft appeared to have increased slightly in size over the years, but this might have been an artifact of the technical improvements in MRI scanning. Intraventricular pressure monitoring and cerebrospinal infusion testing were normal.

We have followed the patient for 2 years, during which the ophthalmological findings have not progressed but the degree of ataxia has clearly worsened.

DISCUSSION

We believe that our patient’s neurologic manifestations are the result of the midbrain cleft. This abnormality was evident on the first brain MRI but was overlooked, perhaps

**FIG. 1.** Axial T2 (A) and FLAIR (B) MRI of our patient show a midline cleft in the midbrain (arrows). Sagittal T2 (C) shows a cleft (arrow) in communication with the fourth ventricle and aqueduct. D. Axial T2 image at the level of the fourth ventricle shows its expansion and rectangular appearance.
because clinicians and radiologists are unfamiliar with this entity. As a consequence, the patient was initially misdiagnosed as having MS.

Six other cases of midbrain cleft have been reported (1–4) (Table 1). Three cases were labeled “mesencephalic clefts” (1,2). Two other cases were labeled “keyhole aqueduct syndrome” (Cases 4 and 5 in Table 1) (3) and 1 had a similar keyhole aqueduct (4) (Case 6 in Table 1). A recent report (5) of a midbrain cleft in the context of bilateral INO is not included as the ocular motor abnormalities were described as acute in onset and the apparent cleft decreased in size with time, suggesting a different pathological mechanism. Also excluded was a much older case of a “posterior diverticulum of the cerebral aqueduct” associated with diplopia from childhood and diagnosed on the basis of pneumoencephalography (6). It was excluded because the patient did not have INO or ataxia, and there was no pathological examination.

Of the 6 cases, 3 (Cases 4, 5, and 6) were examined pathologically (Table 1; Fig. 4) (3,4). Case 5 had developed relentlessly progressive ataxia, which ultimately led to profound immobility and death. Case 4 died of a myocardial infarction; Case 6 died of urinary tract infection. Pathological examination showed a keyhole-shaped cleft at the pontomesencephalic junction that was lined by ependyma and compressed glial tissue. Varying degrees of distortion/destruction of several midbrain nuclei and tracts was seen, particularly involving the medial longitudinal fasciculus (MLF). Atrophy of the pons and cerebellum was noted, and, in Cases 4 and 5, slit-like cavities were observed in the pons, some of which were in communication with the fourth ventricle. Cerebellar degeneration was confirmed by the loss of cortical neurons, gliosis of subcortical white matter, and atrophy of cerebellar nuclei.

Of the 7 reported patients, 4 presented with long-standing symptoms of double vision (1,2,4). In Case 1, this...
was the only symptom (1), but the other patients went on
to develop other neurological features including ataxia
and/or dysarthria. In 3 cases, including the 1 presented here,
the initial presentation was with long-standing ataxia and
dysarthria. In the other 2 cases, ocular motor involvement
appears to have been a late development, unlike our case in
which the INO was found on initial examination (3).

Although ocular findings have been somewhat varied,
INO has been documented in all 7 reported cases. The
authors of the 2 original keyhole aqueduct cases described
INO without specifying whether it was unilateral or bilateral
(3). The clefts are thought to cause the INO through
destruction of the MLF at the level of the midbrain (1,2).
In addition to INO, upgaze paresis and fourth nerve and
partial third nerve palsies have been reported.

Four cases had a progressive clinical course with death
attributed to complications of progressive ataxia. By com-
parison, 2 cases had a relatively static clinical course. In most
cases, symptom onset was in the fourth decade, the latest
presentation occurring at 49 years of age. Brain MRI has
revealed abnormalities similar to those found in our patient.
The midline clefts were partial or complete (Fig. 4). Mis-
diagnosis of MS has been common, as in our patient.

The “keyhole aqueduct syndrome,” (3) a description
applied to cases reported before the availability of brain MRI,
is probably another label for midbrain cleft. All cases had
INO and marked ataxia. The radiological and pathological
findings of both conditions correlate closely (Figs. 4A, C).

The etiology of this condition is unknown. A congenital
cause seems unlikely since presentation is usually delayed
until the fourth decade, with subsequent clinical progression
seen in the majority of cases. Familial occurrence has not
been reported. The time course is consistent with a de-
generative process, supported by the fact that there are
usually clinical or pathological abnormalities remote from
the midbrain, including the pons and cerebellum (3,4).
The cause of the clefts might be disruption of CSF flow
through the aqueduct, an idea supported by the finding of
compression and edema of structures surrounding the clefts
and the pathological cavities in the 3 histological studies
(3,4). This process might be analogous to the slow expan-
sion of a syrinx in the spinal cord or brainstem. Inter-
estingly, the histological features of keyhole aqueducts are
very similar to those of syringes, which mainly affect the
cervicothoracic spine and lower brainstem and almost never
extend above the pons (7). One pathogenetic theory about
the development of a syrinx is that it is related to disrupted
CSF flow via a craniospinal pressure dissociation produced
during Valsalva maneuvers (8). Unlike syringes in the spinal
cord, which are typically ovoid in cross section, syringes in
the medulla or pons typically have a cleft-like appearance.
These clefts usually project laterally rather than in an

<table>
<thead>
<tr>
<th>Case</th>
<th>Year</th>
<th>Age (Yr)*/Sex</th>
<th>Age at Onset of Symptoms and Their Duration Prior to Initial Examination</th>
<th>Clinical Course</th>
<th>INO</th>
<th>Ataxia</th>
<th>Other Ocular Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesencephalic clefts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Current study</td>
<td>2008</td>
<td>44/M</td>
<td>Age 34, ataxia 10 yr</td>
<td>Progressive</td>
<td>Bilateral</td>
<td>Yes</td>
<td>Vertical nystagmus</td>
</tr>
<tr>
<td>1(1)</td>
<td>1996</td>
<td>43/F</td>
<td>Age 30, diplopia (horizontal and vertical) 13 yr</td>
<td>Static</td>
<td>Bilateral</td>
<td>No</td>
<td>Right fourth cranial nerve palsy, upgaze nystagmus, reduced convergence, mild right ptosis</td>
</tr>
<tr>
<td>2(1)</td>
<td>1996</td>
<td>59/M</td>
<td>Unknown, diplopia “very chronic”</td>
<td>Uncertain</td>
<td>Bilateral</td>
<td>Yes</td>
<td>Downgaze nystagmus, reduced upgaze and convergence</td>
</tr>
<tr>
<td>3(2)</td>
<td>1997</td>
<td>67/M</td>
<td>Unknown, diplopia and ptosis since early adulthood, ataxia 10 yr</td>
<td>Progressive</td>
<td>Bilateral</td>
<td>Yes</td>
<td>Bilateral ptosis, upbeat nystagmus</td>
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<tr>
<td>Keyhole aqueduct</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4(3)</td>
<td>1986†</td>
<td>59/M</td>
<td>Age 32, ataxia 27 yr, ptosis 13 yr, diplopia 10 yr</td>
<td>Static, death from unrelated cause</td>
<td>Yes‡</td>
<td>Yes</td>
<td>Bilateral ptosis, upbeat and rotatory nystagmus, ocular bobbing</td>
</tr>
<tr>
<td>5(3)</td>
<td>1986†</td>
<td>58/M</td>
<td>Age 48, ataxia 10 yr</td>
<td>Progressive leading to death</td>
<td>Yes‡</td>
<td>Yes</td>
<td>Vertical nystagmus, anisocoria, horizontal nystagmus</td>
</tr>
<tr>
<td>6(4)</td>
<td>1983†</td>
<td>59/F</td>
<td>Age 32, diplopia and ataxia 27 yr</td>
<td>Progressive, death in 60 s from unrelated cause</td>
<td>Bilateral</td>
<td>Yes</td>
<td>Vertical nystagmus, possible bilateral abducens palsies later in illness</td>
</tr>
</tbody>
</table>

*Age at last report.
†Autopsy-confirmed cases.
‡No information as to whether INO was unilateral or bilateral.
anteroposterior direction (Fig. 4E) (7,9). Why syringes in the brainstem should differ in appearance from those in the spinal cord is not clear, but the answer may lie in differing anatomical structures. Disruption would be likely to extend along lines of greatest weakness such as regions of developmental fusion (10). It is conceivable, therefore, that midbrain clefts are syringes isolated to the midbrain. In our patient, the finding of normal intraventricular pressures and CSF flow on intraventricular monitoring argues against a generalized abnormality of CSF dynamics but would not exclude a local abnormality of CSF flow restricted to the region of the aqueduct. Also, the fact that there was a small syrinx in the cervical cord of our patient is suggestive of a more widespread disorder of CSF flow.

REFERENCES


Nasopharyngeal Carcinoma Presenting With Rapidly Progressive Severe Binocular Optic Neuropathy and Periocular Pain in a Young Man

Kyung-Ah Park, MD, Sei Yeul Oh, MD

Abstract: A 27-year-old man presented with rapid and severe visual loss in both eyes, together with pain behind the eyes. Visual acuities were light perception in both eyes. Pupillary constriction to light was minimal, and ophthalmoscopy results were normal. For a presumptive diagnosis of retrobulbar optic neuritis, he was treated with intravenous corticosteroids, and vision improved transiently. But vision later worsened to no light perception, and MRI revealed bilateral optic nerve enhancement with dural enhancement and thickening in the anterior skull base, sella, and retroclival areas, findings initially interpreted as inflammatory. Nasopharyngoscopy disclosed a soft tissue lesion filling the apex of the nasopharynx and the posterior portion of the ethmoid sinus with associated sinusitis. Biopsy demonstrated a moderately differentiated squamous cell carcinoma believed to have originated in the nasopharynx. This is the first case of bilateral severe optic neuropathy in nasopharyngeal carcinoma invading the skull base. It is reported to emphasize that rapidly progressive severe bilateral optic neuropathy in a young patient with periocular pain need not be caused by inflammation.

doi: 10.1097/WNO.0b013e3181ce2ce7 © 2010 by North American Neuro-ophthalmology Society

Nasopharyngeal carcinoma rarely affects the optic nerves; only 5 cases have been described (1–5). We report a patient with carcinoma who presented with rapidly progressive, severe bilateral visual loss and periocular pain as the initial symptoms.

CASE REPORT

A 27-year-old man was referred to our clinic with a 3-day history of declining vision in both eyes and pain behind his eyes. One year previously, vision was 20/20 in both eyes. The patient had no contributory past medical history.

Examination elsewhere disclosed only light perception in both eyes. For a diagnosis of optic neuritis, he was treated with 1 g intravenous methylprednisolone daily for 3 days. Visual acuity initially improved to counting fingers but worsened several days later.

On our examination, the patient could only perceive light in both eyes. Pupils reacted slowly and weakly to light without a relative afferent pupillary defect. Results of the ocular motility examination were normal. The anterior ocular segments and fundi were normal in both eyes.

MRI delineated bilateral optic nerve and dural enhancement and thickening in the anterior skull base, sella, and retroclival area (Fig. 1). There was no demonstrable mass lesion compressing the optic nerves. T2 imaging demonstrated a low-signal-intensity soft tissue lesion filling the apex of the nasopharynx. There was no bony destruction around the optic canal (Fig. 1). The imaging findings were initially interpreted as indicating sinusitis or an idiopathic inflammatory lesion (“pseudotumor”) involving the sinuses, optic nerves, sella, and skull base.

Nasopharyngoscopic examination disclosed a pink-purple, edematous nasal septum and an ulcerofungating nasopharyngeal mass. Endoscopic biopsy of the nasal mucosa and the sinus wall demonstrated that the mass was a moderately differentiated squamous cell carcinoma (Fig. 2). The patient was referred for chemotherapy.

DISCUSSION

Nasopharyngeal carcinoma is common in southern China, Hong Kong, and Singapore, with the incidence being much higher among Chinese than among Caucasians (6,7). This carcinoma commonly presents with a neck mass, blood-
tinged sputum or rhinorrhea, headache, diplopia, hearing loss, or facial pain (8). Although ophthalmic involvement is not uncommon in patients with nasopharyngeal carcinoma in the late stages of disease, isolated optic nerve involvement is rarely reported as an initial manifestation (1–5).

In our patient, there was sequential bilateral visual loss over the course of 3 days, accompanied by retrobulbar pain. Among previous reports of nasopharyngeal carcinoma initially presenting as visual loss, pain was an associated symptom in 3 patients (2,4,5), and no pain or discomfort was reported in another 3 patients (1,3). In all previous patients, the visual loss was monocular (1–5). In the current report, bilateral and nearly simultaneous blindness was the initial presentation of nasopharyngeal carcinoma, suggesting a rapidly progressive condition.

The blindness in nasopharyngeal cancer is due to optic nerve compression from direct extension of the tumor (1). Four previously reported patients demonstrated a mass lesion around the optic nerve (1,3,4), but there was no demonstrable mass lesion in 2 other patients, and the authors suggested a paraneoplastic effect (2,5). In the current report, direct compression of the optic nerve by the tumor was not obvious, but the optic nerves enhanced as did contiguous regions. Whether the enhancement is due to inflammation or direct infiltration of the optic nerve sheath is uncertain.

FIG. 1. Precontrast (A) and postcontrast (B) T1 axial MRI shows enhancing tumor infiltrating the skull base (asterisk) and enhancing optic nerve sheaths bilaterally (short arrows). C. Postcontrast T1 coronal MRI shows enhancement of both optic nerves (short arrows), the sellar area (long arrow), and the mucosal wall of the sphenoid sinus (arrowheads). D. Postcontrast T1 sagittal MRI shows sellar enhancement (arrow), dural thickening and enhancement in the retroclival area (arrowheads), and irregular enhancement of the mucosal wall of the sphenoid sinus (asterisks). E. Axial CT reveals a soft tissue lesion (asterisk) in the apex of the nasopharynx. F. Coronal CT at the bone window setting demonstrates no bone destruction.
Our patient represents the youngest reported case of optic neuropathy in nasopharyngeal cancer (1–5), although 2 previously reported cases involved patients in their early 30s (2,4). Clinicians usually suspect an inflammatory disorder rather than a malignant process in patients of this age. In 3 previously reported patients (2,4,5), including these relatively young patients, optic neuritis was the initial diagnosis, and corticosteroid treatment was initiated. Transient improvement in vision after steroid therapy delayed the correct diagnosis in our case as well as previous reports (2,4,5).

REFERENCES
Pupillary Dysfunction in an Atypical Case of Mitochondrial Myopathy With Tubular Aggregates

Nadeem Ali, MA, MRCOphth, FRCS (Ophth), Catherine E. Woodward, BSc, Mary Sweeney, BSc, Rahul Phadke, MD, FRCPath, Janice L. Holton, PhD, MRCPath, James Acheson, MRCP, FCRS (Glas), FRCOphth, Gordon T. Plant, MD, FRCP, FRCOphth, Fion D. Bremner, PhD, FRCOphth

Abstract: A 62-year-old man presented with diplopia, ocular ductional deficits, and sluggish pupils. Pupillometry demonstrated large hyporeactive pupils with no evidence of damage to the sympathetic or parasympathetic innervation, indicating a myopathy of the iris musculature. A single large deletion in mitochondrial DNA and characteristic histochemical features on muscle biopsy suggested a mitochondrial cytopathy. However, ultrastructural examination of skeletal muscle fibers showed tubular aggregates (TAs), a finding not reported in mitochondrial cytopathy. The combination of pupillary abnormalities and TAs suggests that mitochondrial dysfunction may not explain the full extent of abnormalities in this case.

doi: 10.1097/WNO.0b013e3181dbfdcd
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The smooth muscles of the iris are reported to be spared in chronic progressive external ophthalmoplegia (CPEO), a mitochondrial cytopathy (1,2). However, pupillary function has never been quantitatively studied in this condition. Moreover, there is no reason why these muscles should be spared from the effects of mitochondrial dysfunction.

We present a case in which ocular ductional deficits were combined with pupil dysfunction and unusual ultrastructural muscle features, raising questions about the nature of this condition.

CASE REPORT

A 62-year-old Indian man presented with an 8-month history of slowly progressive binocular horizontal diplopia. He reported no ptosis, diurnal variation in the diplopia, fatigability, or weakness of his arms or legs. There had been no pain, redness, lid swelling, or proptosis. Medical history was unremarkable, and he was a nonsmoker and non-drinker. There was no family history of neurological disease.

Neuro-Ophthalmological Examination

Our examination revealed best-corrected visual acuities of 20/20 in both eyes, normal color vision, and full visual fields. The pupils were noted to react sluggishly both to light and to the viewing of a near target. Horizontal ductions were moderately reduced in both eyes. In the right eye, there was a reduction in supraduction, and in the left eye, a reduction in infraduction. The patient reported diplopia in all positions of gaze. In primary gaze position, there was a large alternating exotropia with a large left hypertropia (Fig. 1). There was no ptosis, and levator function and orbicularis strength were clinically normal. Intraocular examination revealed visually insignificant posterior cortical cataracts and mild changes in the macular retinal pigment epithelium, findings that were thought to be age related. The peripheral retina appeared normal. Examination of the remaining cranial nerves was unremarkable. Tone and strength were normal in all muscles groups, with neither fatigability nor myotonia.

Laboratory Studies

The patient underwent the following investigations, which produced normal or negative results: acetylcholine receptor antibodies, muscle-specific tyrosine kinase (MUSK) antibodies, striated muscle antibodies, thyroid thyroglobulin antibodies, thyroid microsomai antibodies, and treponemal
serology. Intravenous edrophonium had no effect on his ophthalmoplegia.

**Imaging Studies**
CT of the brain and orbits and MRI of the thymus were normal.

**Electromyography**
Electromyography revealed normal nerve conduction, repetitive stimulation, and single-fiber studies. Muscle sampling showed abundant spiky polyphasic units recorded not only from the orbicularis oculi but also minimally from the extensor digitorum communis, tibialis anterior, and rectus femoris. These findings were suggestive of a mild myopathic process rather than neuromuscular junction dysfunction.

**Muscle Biopsy**
Triceps muscle biopsy revealed the presence of 3 ragged red fibers and more than 10 cytochrome oxidase–negative fibers. Mitochondrial respiratory chain enzyme activity assays were normal. Electron microscopy showed subsarcolemmal accumulations of scattered abnormal mitochondria, many of which contained type 1 paracrystalline inclusions. Tubular aggregates (TAs) were noted in several fibers, some of which contained abnormal mitochondria (Fig. 2). No TAs were seen at the light microscopic level.

**Genetic Analysis**
Mitochondrial genetic analysis confirmed a single large deletion in mitochondrial DNA detected by long-range polymerase chain reaction followed by Southern blotting. Sequencing confirmed the presence of the common deletion of 4,977 base pairs, with break points in the flanking repeats between nucleotides 8,470 and 8,482 and nucleotides 13,447 and 13,459. The patient was therefore diagnosed with CPEO.

**Pupillary Function**
Based on the clinical impression of hyporeactive pupils, infrared video pupillometry was performed and compared with our normative database of measurements from 315 healthy control subjects (3) (Fig. 3; Table 1). Slit-lamp examination showed no abnormality of pupil shape and no iris damage or sector palsy. The resting pupil diameters were significantly larger than expected for his age (outside the 95% upper limit of the normal range) both in darkness and in light. The amplitudes of the responses of both pupils to a transient light stimulus were attenuated (below 95% lower limit of the normal range). The pupillary miosis to the viewing of a near target was also attenuated (although it could only be reliably recorded from the right eye), and there was no light-near dissociation. Startle responses (mydriasis following a sudden noise) were present but sluggish in both eyes.

Pharmacological testing demonstrated a normal mydriatic response to topical 4% cocaine drops and no cholinergic supersensitivity to 0.1% pilocarpine drops. Pupillometry thus confirmed that both pupils were abnormally large with sluggish responses to light, and near stimuli, and sudden

**FIG. 1.** Our patient displays a left hypertropia and exotropia in primary gaze and no ptosis.

**FIG. 2.** Electron microscopy of triceps muscle biopsy. A. Subsarcolemmal accumulations of abnormal mitochondria (M). B. Abnormal mitochondria (m), and tubular aggregates (TA) in the same fiber.
noise. Without evidence of damage to the sympathetic or parasympathetic innervation, myopathic dysfunction was suggested.

**DISCUSSION**

CPEO describes a spectrum of conditions characterized by bilateral ptosis and global restriction of eye movements (4). It represents the commonest ocular manifestation of the mitochondrial myopathies (5) and can occur in isolation or in association with nonocular features (6).

However, there are several features of the present case that are not typical of CPEO. First, the ductional deficits were not symmetrical in the 2 eyes. The eyes were markedly misaligned, whereas in CPEO, they are usually aligned. Although asymmetric ophthalmoplegia has been rarely described (4,7), its extent, when accurately measured, is usually small. One study found that in 68% of muscle pairs, the degree of asymmetry was less than 5°; asymmetry greater than 18° occurred in less than 2% of muscle pairs (8).

Second, our patient lacked ptosis. Bilateral ptosis is almost always found in CPEO and is the presenting complaint in up to 90% of cases (4). Cases of CPEO without ptosis have only rarely been described (9).

Third, involvement of the iris musculature has not been reported in CPEO. In the present case, pupillometry confirmed the clinical impression of large sluggish pupils. The clinical signs, pupillometric measurements, and pharmacological tests indicated intact innervation of the sphincter and dilator iris muscles but poor contractility due to an intrinsic myopathic process. Given the genetic and histological evidence supporting a diagnosis of mitochondrial cytopathy, it seems reasonable to conclude that in this unusual case, the smooth muscles of the iris may have been affected by this single large mitochondrial DNA deletion. The large resting diameters of these pupils suggest a greater

**TABLE 1.** Pupillometric measurements in our patient.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Right pupil</th>
<th>Left pupil</th>
<th>Normal range (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dark diameter (mm)</td>
<td>7.80</td>
<td>7.01</td>
<td>4.00–7.25*</td>
</tr>
<tr>
<td>Light diameter (mm)</td>
<td>6.58</td>
<td>5.53</td>
<td>1.80–3.82*</td>
</tr>
<tr>
<td>Amplitude of light response (mm)</td>
<td>0.75</td>
<td>0.98</td>
<td>1.79–3.95 (R)†</td>
</tr>
<tr>
<td>T_{3/4} redilatation time (seconds)</td>
<td>4.96</td>
<td>5.28</td>
<td>0.30–2.72 (R)‡</td>
</tr>
<tr>
<td>Amplitude of near response (mm)</td>
<td>0.58</td>
<td>Poor quality recording</td>
<td>None defined</td>
</tr>
<tr>
<td>Startle response</td>
<td>Present</td>
<td>Present</td>
<td>None defined</td>
</tr>
</tbody>
</table>

The normal ranges are for healthy control subjects. * = age matched; † = expected values given the observed resting diameters in the dark; ‡ = amplitude matched or the range of measurements found in healthy control subjects when stimulus intensity is adjusted to produce light responses of similar amplitude to those seen in this patient.
impact of this genotype on sphincter muscle fibers than on dilator muscle fibers.

We were struck by the apparent similarity between the pupil findings in our case and those associated with myotonic dystrophy (dystrophia myotonica, DM), another condition that can produce ophthalmoplegia. The pupils in patients with DM type 1 are often small or of medium size, with sluggish low amplitude light responses. They show the presence of a startle response, no light-near dissociation, and no cholinergic hypersensitivity (10). However, the present case had no other clinical features suggestive of DM (family history, grip myotonia, iridescent lens opacities), and molecular genetic testing for the recognized mutations associated with DM1 or DM2 was negative, thus making a co-occurrence of these 2 genetic disorders unlikely.

A strikingly unusual feature of the present case was the finding of TAs on electron microscopy of the muscle biopsy. TAs in skeletal muscle fibers can occur as a nonspecific finding in a variety of conditions such as periodic paralysis, myotonic disorders, hyperaldosteronism, chronic use of drugs, and alcoholism. In addition, TAs have also been found more specifically in exercise-induced cramps, myasthenic syndromes, and dominantly or recessively inherited familial myopathies (11). Abnormal pupils have been reported in some of the cases of familial TA myopathies (12,13). However, TAs are not recognized as a feature of mitochondrial cytopathies. There is only a single report of a patient with distal myopathy who was found to have multiple deletions of mitochondrial DNA and a high density of TAs (14).

The fact that pupil involvement is not seen in typical CPEO, together with the finding of tubular aggregates on muscle biopsy in our patient, suggests that mitochondrial cytopathy might not be the full extent of the abnormality here. Perhaps this patient has a combination of a mitochondrial cytopathy and an inherited disorder of other origin. Additionally, this case raises the question as to the extent of undetected smooth muscle involvement in mitochondrial cytopathy.

ACKNOWLEDGMENT

The patient shown in Figure 1 provided written consent for the image to be published.

REFERENCES

The Chiasmal Spur

Carol Chen, BSE, Kai Tang, MD, Maozhi Zhang, MD, Song Lin, MD

Abstract: A 51-year-old woman underwent craniotomy for removal of a pituitary tumor. At surgery, anomalous tissue was found projecting forward from the anterior angle of the optic chiasm. Termed “the chiasmal spur,” this anomaly has been described previously in 5 patients, all as an incidental finding at autopsy. Our case is the first instance of the chiasmal spur being discovered and photographed intraoperatively.

doi: 10.1097/WNO.0b013e3181de897b
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A 51-year-old woman reported oligomenorrhea, fatigue, and decreased vision in her left eye. Examination revealed normal acuity and visual fields bilaterally. The optic discs were normal in appearance. Brain MRI demonstrated a pituitary tumor, and the patient underwent a left transfrontal craniotomy.

During surgery, both optic nerves were exposed and it was discovered that additional tissue extended anteriorly 1 cm from the midline surface of the chiasm (Fig. 1). This tissue formed a spur midway between the optic nerves and was slightly adherent to the pituitary tumor. The spur tapered to a rounded point before reaching the sphenoid bone and appeared continuous with the optic nerves and chiasm. The pituitary adenoma was subtotally resected with care taken not to damage the spur in order to avoid any possible visual loss. The postoperative course was uneventful, and the patient’s acuity and visual fields remained normal.

In 1961, Ellis et al (1) reported 4 cases of this optic chiasmal anomaly at autopsy and coined the term “chiasmal spur.” The patients’ causes of death appeared neither to be related to each other nor to the presence of the spur. In each instance, the optic nerves appeared normal, and the spur extended 0.4–1.0 cm from the anterior margin of the chiasm (Fig. 2). The relationship between visual function and the spur was not documented in any patient. Histological analysis revealed myelinated nerve fibers arranged in a parallel longitudinal pattern (Fig. 3). In 2 of the reported cases, an additional process extended 0.2 cm from the posterior margin of the chiasm at the midline. Ellis et al (1)
pointed out that in 1934, Volland (2) had first described this anatomic anomaly as an incidental finding at autopsy in a patient with bronchial carcinoma.

The etiology of chiasmal spur is uncertain. Ellis et al (1) reviewed Wilbrand’s observation made in 1904 that axons from the inferonasal aspect of the optic nerve diverged into the contralateral nerve before reaching the chiasm. This fiber bundle has become known as Wilbrand’s knee. The authors speculated that the chiasmal spur was formed by isolation and fusion of Wilbrand’s knee from each optic nerve.

In 1997, Horton (4) demonstrated in both primates and humans that Wilbrand’s knee does not exist. Rather, this arrangement of retinal fibers forms gradually over a period of many years following monocular enucleation (Wilbrand’s 2 patients had each suffered loss of an eye). Presumably, this shift in fibers occurs due to shrinkage and distortion of chiasmal anatomy. In addition, Lee et al (5) reported 3 patients who underwent resection of one optic nerve at the optic nerve-chiasm junction, and postoperatively, no perimetric evidence was found to support the existence of Wilbrand’s knee.

A more likely explanation for chiasmal spur formation relates to development of retinal axon distribution within the optic chiasm. Since histologic analysis of the chiasmal spur revealed myelinated nerve fibers, it is likely that the anomaly found in our patient consists of neural tissue as well. The determination of crossed and uncrossed fibers within the optic chiasm is a complex process, which is not fully understood (6,7). Within the retina, gene expression of specific transcription factors and guidance receptors regulate the uncrossed projections. However, the means by which retinal axons are guided across the midline are still unclear. In addition, there appear to be transcription factors that affect development of the ventral diencephalon, which, in turn, also plays a role in axon divergence at the chiasm. Presumably, some aberration in the genetic programming of transcription factors and receptor proteins could lead to formation of the chiasmal spur.

While the chiasmal spur has been reported previously, our case is noteworthy as it is the first documented and photographed in the living patient. The presence of normal acuity and visual fields in our patient suggests that this anomaly has no detrimental effect on visual function. Given previous histologic findings that the spur contains

**FIG. 2.** Appearance of the chiasmal spur in 3 patients studied at autopsy. (Reproduced with permission from reference 1.)

**FIG. 3.** Myelinated nerve fibers surrounded by pia and arachnoid forming the chiasmal spur. Luxol fast blue, ×24. (Reproduced with permission from reference 1.)
myelinated nerve fibers, it would be prudent to avoid damaging it at the time of surgery.

REFERENCES
**Monocular Nasal Hemianopia From Atypical Sphenoid Wing Meningioma**

Rebecca C. Stacy, MD, PhD, Frederick A. Jakobiec, MD, DSc, Simmons Lessell, MD, Dean M. Cestari, MD

**Abstract:** Neurogenic monocular nasal field defects respecting the vertical midline are quite uncommon. We report a case of a unilateral nasal hemianopia that was caused by compression of the left optic nerve by a sphenoid wing meningioma. Histological examination revealed that the pathology of the meningioma was consistent with that of an atypical meningioma, which carries a guarded prognosis with increased chance of recurrence. The tumor was debulked surgically, and the patient’s visual field defect improved.

doi: 10.1097/WNO.0b013e3181de8b56
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**FIG. 1.** Automated visual fields demonstrate a nasal defect in the left eye.
A 55-year-old woman presented with sudden painless blurred vision of the left eye. The patient had a history of hypertension, diabetes, and hypercholesterolemia, but her ophthalmic and neurologic histories were negative. She was evaluated elsewhere within 2 days of the onset of her symptoms, and nonarteritic anterior ischemic optic neuropathy (NAION) was diagnosed. We evaluated her 1 week after the onset of symptoms. The patient’s visual acuity was 20/15 in the right eye and 20/25 in the left eye, with dyschromatopsia and a relative afferent pupillary defect in the left eye. No strabismus or motility disturbances were detected, and the left eye had 2 mm of proptosis. Automated perimetry showed a full field in the right eye and a nasal defect in the left eye (Fig. 1). There was temporal pallor of the left optic nerve with no disc edema.

Brain MRI with gadolinium revealed a tumor involving the left sphenoid wing measuring 3.3 × 3.6 × 4 cm with extension into the left cavernous sinus and orbital apex, compressing the left optic chiasm and left side of the optic nerve (Fig. 2). The tumor was debulked via a left frontotemporal craniotomy. Postoperative neuro-ophthalmologic examination showed that the vision was 20/20 in the left eye with a persistent relative afferent pupillary defect. Repeat visual fields showed improvement of the left nasal field defect (Fig. 3).

Histopathologic evaluation of the lesion revealed a meningioma proliferating in a hypercellular sheet-like fashion with interspersed hemorrhage (Fig. 4A) and foci of fresh necrosis, which lay adjacent to hyalinized fibrosis (Fig. 4B). Some regions manifested the whorl-like morphology of a meningoepithelial meningioma (Fig. 4C), while others contained spindle cells typical of a fibrous meningioma. The nuclei within some of the tumor cells were atypical manifesting prominent nucleoli (Fig. 4D). The findings of sheeting, hypercellularity, atypical nuclei with prominent nucleoli, and areas of necrosis were consistent with a diagnosis of atypical meningioma (1,2). A postoperative MRI demonstrated residual tumor abutting the intracranial

**FIG. 2.** Postcontrast T1 axial (A) and coronal (B) MRI show compression of the lateral aspect of the left optic nerve (arrow).

**FIG. 3.** Postoperative left visual field reveals partial resolution of the nasal field defect.
portion of the left optic nerve. The patient is currently scheduled for treatment with radiation oncology.

Unilateral nasal field defects are extremely rare, and when organic, are often associated with optical phenomena such as subcapsular or traumatic cataract (3,4). Nasal field defects have rarely resulted from aneurysms and mass lesions compressing the temporal side of the optic nerve (5–8). In one case series, nasal field defects due to a dolichoectatic carotid artery, optochiasmatic arachnoiditis, meningioma, or pituitary tumor were associated with optic nerve compression and compromised visual acuity (9). In contrast to our patient’s defect, in these cases, the superior portions of the nasal fields were often retained. When the meningioma compressing the optic nerve was debulked, the patient’s field defect and acuity improved. This is consistent with previous reports.

Histological evidence shows that retinal ganglion cell axons that do not cross at the chiasm acquire their temporal arrangement in the optic nerve before they reach the optic foramen (10). Therefore, a sphenoid wing meningioma or other lesion that compresses the temporal side of the optic nerve would affect the nondecussating fibers resulting in a nasal field defect. With long-standing compression, temporal nerve pallor, as was apparent in our patient, may result. NAION was a diagnostic consideration in this patient with a history of sudden vision loss, hypertension, and diabetes. However, the absence of optic disc swelling at the time of presentation made the diagnosis of NAION unlikely (11). The onset of visual symptoms, which the patient interpreted as sudden, was almost certainly pseudosudden since optic atrophy was already present.

**FIG. 4.** Pathology of the atypical meningioma. A. Area of sheeting with no fascicular or whorled cellular patterns. B. Focus of necrosis (arrows) surrounded by hyalinized fibrous tissue indicating probable healed necrosis. C. Whorl-like pattern common in meningoepithelial tumors. D. The nuclei are atypical and have prominent nucleoli. (Hematoxylin and eosin, (A/B) × 100; (C) × 200; and (D) × 400).


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Histopathologic review of the patient’s lesion revealed an atypical meningioma, which accounts for approximately 15% of meningiomas and are classified as World Health Organization Grade II lesions (12). The sheeting architecture, macronucleoli, and hypercellularity that may reflect a dedifferentiated state can be interspersed with more benign pathologic characteristics (2). Because atypical meningiomas have a higher chance for recurrence than the more common benign lesions, approaching 40% as compared with 12% for Grade I meningiomas (1), all areas of the biopsied meningioma must be sampled and carefully examined to avoid overlooking an atypical meningioma. Total resection of the lesion can reduce the rate of recurrence and adjuvant fractionated radiotherapy or stereotactic radiosurgery may help to control regrowth (13).

REFERENCES
Transient Downbeat Nystagmus After Intravenous Administration of the Opioid Piritramide

Morphine may cause vertical nystagmus after epidural or intrathecal administration (1–4) and rarely after intravenous administration (5,6). We report a patient who developed downbeat nystagmus almost immediately after intravenous administration of the opioid piritramide.

A 78-year-old man developed acute pain and weakness of the right leg. He had a medical history of hypertension and hypercholesterolemia and had suffered a left hemispheric cerebral infarction with a persistent spastic right hemiplegia and aphasia 19 years earlier.

On the day of admission he received an intravenous bolus of 15 mg of piritramide to relieve pain. Minutes later a nurse noticed that downbeat nystagmus had appeared in primary gaze position and increased in intensity on downward gaze, a phenomenon we confirmed. The patient denied any visual symptoms. Nausea, vertigo, and vomiting were not present. On neurologic examination, no abnormalities were noted apart from the nystagmus. Electrolyte, creatinine, and liver enzyme levels were normal.

The nystagmus had disappeared on reexamination 2 hours later. Brain MRI showed only an old infarct in the left cerebral hemisphere.

We attribute the downbeat nystagmus to piritramide because of the immediate onset of the nystagmus after administration and its spontaneous resolution. Other diseases causing downbeat nystagmus, such as brainstem or cerebellar infarction, were ruled out by brain MRI. Lesions of the labyrinth or the vestibular nerve or disorders of the craniocervical junction were not noted. Other drugs known to induce downbeat nystagmus, such as anticonvulsants or lithium, had not been given.

Nystagmus or vertigo after epidural administration typically occurs with a latency of approximately 7–10 hours from drug administration (6,7). In our patient, nystagmus began only minutes after administration because opioids cross from blood to brain faster than from epidural space to brain.

Central nervous system structures involved in the mechanism of downbeat nystagmus after administration of opioids presumably are the cerebellum and the vestibular nuclei. After administration of pethidine, healthy individuals showed typical cerebellum-associated symptoms such as dysarthria and intention tremor (8). Lesions of the vestibulocerebellum are known to induce downbeat nystagmus (9). Opioid receptors, particular the receptors, are expressed in the cerebellum (10). The activation of receptors by piritramide causes an inhibition of cerebellar neurons, which might evoke downbeat nystagmus.

Opioid receptors are also located in the medial vestibular nucleus (11). Activation of these receptors has evoked inhibition of the tonic discharge of neurons, possibly leading to a vertical upward drift, which produces a compensatory fast downward eye movement, thus downbeat nystagmus (8).

In patients with suspected opioid toxicity, administration of naloxone should reverse the manifestations and confirm the diagnosis.

REFERENCES

Pompe disease is a lysosomal disorder caused by deficiency of acid α-glucosidase (GAA) that leads to accumulation of glycogen in multiple tissues. Enzyme replacement therapy (ERT) with alglucosidase alfa (Myozyme; Genzyme Corporation, Cambridge, MA) is the first treatment for this lethal disorder. We report improvement of ptosis in a 17-year-old boy with nonclassic infantile-onset disease in response to increased dosage of ERT.

The patient presented at 6 months of age with cardiomyopathy and proximal skeletal myopathy. Pompe disease was diagnosed at 9 months of age based on muscle biopsy showing vacuolar storage of glycogen and decreased GAA activity in muscle and lymphocytes. In addition to skeletal and respiratory muscle weakness, he displayed slowly progressive, variable bilateral ptosis (Fig. 1). Pupillary and ocular motility findings were normal. Results of acetylcholine receptor antibody testing were negative.

At age 13 years and 4 months of age, the patient was treated with alglucosidase alfa at a dose of 20 mg/kg every other week based on recommendations in the package insert (1). The alglucosidase alfa therapy stabilized but did not improve his skeletal and respiratory muscle weakness. The degree of ptosis appeared to be unaffected (Fig. 2).

After 2 years of ERT at this dosage, he demonstrated significant decline in his muscle strength. Besides progression of the Pompe disease, there was no explanation for this decline. At the age of 16 years and 8 months, the alglucosidase alfa dosage was increased to 40 mg/kg every other week. Within 6 months, he showed improvement in muscle function and partial resolution of ptosis (Fig. 3). The ERT infusions were well tolerated. Antibody titers to alglucosidase alfa remained <1:800. He did not develop proteinuria or show any suggestion of immune complex disease.

FIG. 1. Our patient with Pompe disease before treatment. At age 14 months (A), 10 years (B), and 12 years (C), ptosis is progressing.

FIG. 2. Treatment with 20 mg/kg alglucosidase alfa biweekly has produced no improvement in ptosis at age 13 years (A) and 15 years (B).

FIG. 3. Treatment with 40 mg/kg alglucosidase alfa biweekly has produced improvement in ptosis at age 17 years.
This patient illustrates the need for individualization of ERT dosage based on clinical response.

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P.S.K. has received research/grant support and honoraria from Genzyme Corporation (Cambridge, MA) and is a member of the Pompe Disease and the Gaucher Disease Registry Advisory Board for Genzyme Corporation. R.C. has received research/grant support and honoraria from Genzyme Corporation. rhGAA, in the form of Genzyme’s product, Myozyme, has been approved by the U.S. Food and Drug Administration, Health Canada, and the European Union as therapy for Pompe disease. Duke University and inventors for the method of treatment and predecessors of the cell lines used to generate the enzyme (rhGAA, Myozyme) receive royalty payments pursuant to the university’s policy on Inventions, Patents and Technology Transfer.

REFERENCE

Choroidal Infarction in Fulminant Idiopathic Intracranial Hypertension

We describe a case of idiopathic intracranial hypertension (IIH) in which visual loss is partially attributed to choroidal infarction. We believe that this phenomenon has not been reported previously.

A 20-year-old white woman complained of severe headaches with nausea, photophobia, and pulsatile tinnitus. During the previous week, she had noticed rapidly progressive visual loss in both eyes with severe constriction of her peripheral visual field. Review of systems was remarkable only for a recent weight gain of 20 pounds over the previous year.

On our examination, body mass index was 26.6 kg/m² and blood pressure was 110/68 mmHg, and results of the neurologic examination were normal. Visual acuity was 20/20 in the right eye and 20/30 in the left eye. Automated and kinetic visual fields showed bilateral constriction with an inferior nasal defect and enlarged blind spot in the right eye and an inferior altitudinal defect in the left eye. Ophthalmoscopic examination (Fig. 1) showed bilateral severe optic disc edema with peripapillary hemorrhages and nerve fiber layer ischemic whitening. In the left eye, there was an area of juxtapapillary whitening extending to the macula, which appeared to be in the deep retina or choroid.

Fluorescein angiography (FA) showed normal choroidal filling 25 seconds after injection and normal retinal perfusion, ruling out a branch retinal artery or cilioretinal artery occlusion (Fig. 2A). However, indocyanine green (ICG) videoangiography (Fig. 2B) demonstrated a choroidal perfusion defect matching the juxtapapillary whitening in the left fundus, confirming a choroidal infarction.

We attributed the ophthalmic findings to raised intracranial pressure (ICP) with severe papilledema in both eyes, choroidal infarction, and anterior ischemic optic neuropathy (AION) in the left eye.

The diagnosis of IIH was confirmed by normal brain MRI and magnetic resonance venography (MRV) and by a cerebrospinal fluid (CSF) opening pressure of 560 mm H₂O with normal CSF contents (1). A diagnostic lumbar puncture relieved her headaches immediately, and treatment with 500 mg oral acetazolamide twice a day was begun. Her visual function, however, remained poor, and she underwent bilateral sequential optic nerve sheath fenestrations (ONSFs) 8 and 21 days later.

The headaches did not recur. The optic disc edema resolved, and she developed optic disc pallor in both eyes. The juxtapapillary whitening resolved within 2 weeks of the ONSFs. The altitudinal defect remained unchanged in the left eye, and the visual field improved in the right eye but remained constricted (Fig. 3). Final visual acuity was 20/20 in both eyes.

Our patient developed severe bilateral papilledema in the setting of fulminant IIH (2) and had visual loss related to visual field constriction from papilledema, choroidal infarction, and AION. Although the anatomy of the short posterior ciliary arteries that vascularize the choroid around the optic disc might logically explain the occurrence of a choroidal infarction in acute and prominent papilledema, we could not find any previous report of such a complication in the setting of severe papilledema. However, 5 patients with presumed choroidal infarction have been

FIG. 1. Bilateral optic disc edema with papillary cotton wool spots. In the left eye, there is an area of whitening extending to the macula and located deep to the retina.
reported previously as a complication of ONSF performed for papilledema (3–6). Immediate recognition of the mechanism of visual loss in patients with papilledema is essential in making appropriate therapeutic decisions. Choroidal infarction should be added to the list of rare complications of severe papilledema.

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REFERENCES
Superior Oblique Myokymia Following Endoscopic Arterial Ligation for Epistaxis

Ligation of the anterior ethmoidal and sphenopalatine arteries is a common surgery for control of intractable epistaxis. Injury to the extraocular muscles and transient diplopia are potential complications of this procedure (1), and several cases of superior oblique palsy (SOP) have been reported (2–4). Transient superior oblique muscle dysfunction may be masked by decreased visual acuity in the setting of postoperative swelling (3). We report a case of superior oblique myokymia (SOM) occurring shortly after endoscopic arterial ligation for epistaxis, speculating that it shares a common ischemic pathogenesis with SOP.

A 38-year-old man who underwent endoscopic ligation of the right sphenopalatine and anterior ethmoidal arteries for recurrent epistaxis complained of “jumping” of his right eye starting within a month after the surgery. He described countless daily episodes of vertical oscillopsia in the right eye lasting seconds and accompanied by binocular vertical diplopia. Brain/orbit MRI and MRA were normal. When his symptoms persisted, he consulted us 16 months postoperatively. We noted a prominent torsional microtremor of the right eye consistent with SOM as the only abnormality.

Given the temporal correlation between the endoscopic surgery and onset of symptoms, we believe that the surgery was a contributing if not causative factor of SOM in this case. Several mechanisms have been proposed regarding the etiology of SOP following anterior ethmoidal and internal maxillary artery ligation for epistaxis. Couch et al (2) reported 2 cases of SOP, attributing it either to hematoma leading to perioveal elevation and trochlear displacement, posterior orbital hematoma causing compression of the fourth cranial nerve, or superior oblique muscle ischemia. Jacobson and Pesicka (3) reported a case of SOP following ligation of the internal maxillary, superior ethmoidal, and posterior ethmoidal arteries. The palsy resolved within 5 months, and they suggested ligation-induced muscle ischemia as the cause.

Lee (5) reported 2 cases of SOM preceded by SOP, speculating that the SOM represented a postdenervation phenomenon of the superior oblique muscle or aberrant nerve regeneration following a fourth cranial nerve lesion. We believe that our patient developed permanent SOM following arterial ligation as a consequence of ischemia to the fourth cranial nerve at the orbital level. The SOM in this case may have represented a milder form of ischemic injury than that resulting in SOP.

REFERENCES
**Vision and Driving: The United States**

Chris A. Johnson, PhD, Mark E. Wilkinson, OD

**Abstract:** Minimal visual standards for obtaining driving licensure in the United States principally use 2 measures: visual acuity and visual field. Although research studies have established a correlation between performance on these measures and safe driving, the correlations are weak and mostly retrospective. These measures remain in place in screening centers largely because they (especially visual acuity) are practical. A newer test of visual attention, called the useful field of view, may be more predictive of safe driving than the traditional measures, but it has not been widely applied in licensing bureaus.


Driving is a complex multifaceted activity in which visual performance is a critical feature. Research projects utilizing more detailed and thorough approaches have produced new insights into the role of vision during the driving task and the use of technological advances to improve the driving experience for individuals with visual impairments. We review the research directed toward vision and driving with an emphasis on visual acuity, contrast sensitivity, color vision, and visual fields. Although attention, visual search, decision making, and other cognitive functions are also clearly involved with driving performance, these components are reviewed elsewhere (1,2).

While it is a fundamental responsibility of licensing bodies to identify drivers with impairments that place them at an unacceptable risk for crashes, the decisions they make about licensing must be legally and morally defensible and must not unfairly restrict the mobility of disabled or aging drivers. It is important, therefore, that the licensing criteria for visual fitness be based on scientific evidence establishing their effectiveness and predictive value for unsafe driving performance, particularly for older drivers (1). Surprisingly, there is no rigorous evidence to support the hypothesis that vision screening leads to a reduction in motor vehicle crashes involving older drivers or that a specific cutoff value for vision performance improves safety (2). This seeming conundrum is probably resolved by acknowledging that driving safety depends less on what the driver sees than on how quickly, adequately, and accurately he responds to what is seen (2).

Many review articles have evaluated the relationships among driving performance, vision, decision-making behavior, risk-benefit analysis, and related factors (3–9); but few have incorporated these issues within the context of visual performance, driving demands, and visual and cognitive impairment questions that arise during the course of an eye examination. Following a brief review of visual factors affecting driving, we discuss the issues directly pertinent to eye care providers.

**HISTORICAL PERSPECTIVE**

The foundations of research on vision and driving can be traced back to the Transactions of the Section on Ophthalmology of the American Medical Association’s Seventy Sixth Annual Session in Atlantic City, New Jersey, on May 25–29, 1925 (10). The Committee on Visual Standards for Licensure to Operate a Motor Vehicle recommended that driver license applicants demonstrate a visual acuity of at least 20/50 in one eye and at least 20/100 in the fellow eye, with or without glasses. Applicants with visual acuity worse than 20/100 in the poorer eye could be qualified to drive a motor vehicle by a special board under certain circumstances. Diplopia would disqualify an applicant from obtaining a license to operate a motor vehicle.

The next formal report concerning vision standards for driving appeared on October 16, 1937 in the Organization Section of the Journal of the American Medical Association (Vision Standards for Licensure to Operate a Motor Vehicle) (11), which indicated that the 1925 recommendations for a board of physical licensure in each county had proved to be impracticable and had therefore not been embodied into law or practice. The report also indicated that standards of good vision necessary for efficient operation of a motor vehicle...
vehicle could not be arbitrarily fixed because the problem of safety also depended on factors such as the driver’s natural aptitude, experience, and general mental and physical fitness. The lack of good vision might be compensated for by a high degree of efficiency in aptitude, experience, and mental and physical fitness. The report modified the vision standard for driving licensure to 20/40 or better in one eye (with or without glasses) and 20/100 or better in the fellow eye (with or without glasses). It recommended a horizontal extent of the visual field of at least 45° to both sides of the point of fixation; a binocular single vision; and the ability to distinguish red, green, and yellow. A limited driving license could be obtained with a visual acuity of at least 20/65 in the better eye, a field of vision extending at least 125° horizontally in one eye, and the absence of diplopia. Personal qualities that could compensate for minor defects of vision would have to be highly rated in those to whom a limited license was to be issued.

The 1937 report was followed by investigations performed by Burg (12–15) in landmark studies published in the 1960s. These studies evaluated a large population of California drivers on an extensive battery of vision, reaction time, and decision-making tests. This work served as a basis for establishing vision requirements for a driving license, although many questions arose concerning the individuals selected for inclusion in the study, the methodology used in some of the test procedures, and the analysis procedures used in evaluation of the data. Burg’s work (12–15) was a retrospective study of the association of vision and cognitive properties with driving accidents and convictions; no validation or prospective evaluations were performed. Subsequent studies of vision and driving have explored the influence of visual impairment on driving, the use of devices to accommodate disabilities, and cognitive and decision-making aspects of driving (1,2,7,16–93). Using driving simulators, population-based studies, closed road tracks, and retrospective reviews of driving accidents and convictions, they have provided more sophisticated information on visual performance and driving behavior, as described in a later section of this article. The factors most often considered are visual acuity, contrast sensitivity, visual fields, and color vision.

Visual Functions and other Factors Related to Driving

Most studies indicate that visual acuity, contrast sensitivity, visual fields, and color vision have the strongest relationship to driving performance (12–43). We will provide a summary of results from these investigations, and direct the interested reader to the more comprehensive reviews (6–11). In the past, most research was directed at establishing the relationship between vision and driving among individuals with normal vision. Only recently, there have been efforts toward evaluating the driving abilities of individuals with vision impairments (1,44–55).

Visual Acuity

Visual acuity is the most universal vision requirement for obtaining a driving license. Tests of visual acuity can be administered rapidly with a standardized test procedure by personnel with minimal visual testing skills. It is acknowledged as critical for interpreting traffic signs and detecting road hazards. In the United States, most jurisdictions require an unaided or best-corrected visual acuity of 20/40 in the better eye (7). Most of the signage and other roadside information have been designed to be read by individuals with 20/40 or better visual acuity who are operating a motor vehicle at or below the speed limit.

A number of studies have evaluated the consequences of driving with reduced visual acuity produced by cataract or other ocular and neurologic diseases or by artificially degrading vision by means of lenses or translucent devices in persons with normal visual acuity (46,49,50,53–55). These studies have mostly been performed retrospectively by reviewing visual acuity status and traffic accidents and convictions in the general population, the elderly, the young, and those with physical or mental impairments. Prospective studies have measured driving performance on a closed road track or in a driving simulator (1,46–55). Reductions in visual acuity produce impairments in certain aspects of driving related to specific driving tasks, such as recognition of road signs, road hazards, highway markings, and objects entering the roadway (29).

Contrast Sensitivity

Evans and Ginsburg (17) and Ginsburg (18) have reported that contrast sensitivity is an important factor in being able to distinguish the legibility of highway signs and other properties of functional vision that are associated with driving, such as recognition of road signs, hazards, traffic signals, and indicator markers. In bad weather and in night driving, highway signs, road hazards, animals, and pedestrians have low contrast. For this reason, many studies have incorporated the detection and discrimination of low-contrast objects as part of their driving research (44).

Night Vision

At night, highways and intersections are not as well delineated. The span of usable vision is smaller due to nonuniform lighting of the highway and the short distance for which the headlights of a vehicle can illuminate the roadway. Paradoxically, drivers tend to maintain nighttime driving speeds at nearly the same level as daytime driving speeds (56–60). Accidents are more than twice as frequent at night (56–60). Regrettably, there has been very little useful research on night time driving.
**Visual Fields and Attention**

Early investigations did not find a meaningful relationship between peripheral vision and accident and conviction reports (13). Among the many factors responsible for this lack of a relationship are the low prevalence of visual field loss in the general population; self-restriction of driving by individuals with ocular or neurologic disorders; the use of peripheral vision test equipment with high false-positive and false-negative rates; and the lack of reproducibility, confirmation, and validation of test findings (19).

But with a visual field instrument of known performance characteristics, a study (19) finally found that drivers with significant visual field loss in both eyes had more than twice as many accidents and convictions as drivers with normal visual fields or loss in only one eye. Subsequently, many studies reported a relationship between visual field loss and driving performance (20–31). When the binocular visual field was reduced to 50°–60° in diameter, impairments in driving performance were noted (19,20,22). However, more recent investigations have found that even relatively minor amounts of visual field loss are related to deficits in driving performance (22,23).

The devices that perform clinical visual field testing rely on the subject’s ability to detect a single stimulus superimposed on a uniform background. Because driving is much more complex, investigators (32–37) have developed a test known as the useful field of view (UFOV), which combines peripheral target detection with measurements of reaction time, the ability to perform multiple tasks (including simultaneous central and peripheral target recognition), and the ability to localize targets and distinguish one from another (see Anticipated Future Developments). The intent of the UFOV test is to provide a more powerful surrogate of the visual and cognitive tasks encountered during driving. Studies (32–37) have verified that this test is useful in identifying task performance difficulties associated with driving impairments.

**Color Vision**

The role of color vision in safe driving is complex because deficient color vision can be congenital or acquired, stable or progressive, partial or complete, and affect primarily red (protan), green (deutan), blue (tritan), or all color sensitive visual mechanisms. Moreover, color is not the only visual attribute used to distinguish a critical visual target. Individuals with red (protan) deficiencies have greater difficulty seeing red traffic signals and automobile tail lights at night, thereby producing a higher risk of traffic accidents (39–41). Individuals with protan (red) and deutan (green) deficits have greater difficulty recognizing traffic signal colors and the conspicuity of signs and signals (39,41–43). Many sunglass manufacturers do not adhere to the recommended specifications for tint colorations and produce spectacles that create significant difficulties for color deficient observers (38).

Although color vision performance is not a component of the standard for obtaining a standard driving license in the United States, it is a component for obtaining a commercial vehicle driving license. To obtain a US commercial driving license, the driver must be able to distinguish traffic control signals and devices showing red, green, and amber colors. Some European countries use it as a component for obtaining a standard driving license.

**Other Factors**

Even if visual modalities are intact, their integration with auditory, memory, and other sensory information can be an especially difficult task for youthful, elderly, or neurologically impaired individuals. This lack of integration may lead to an increase in vehicular accidents (61–64). For example, studies have shown that cellular telephone use during driving disrupts sensory tasks and driving performance (61–64). The effect of instruction, rehabilitation, and the use of assistive devices on driving performance has been controversial (11,24,25,30,44,48–50,54,55,58,61–64,70,71,77,83,92). For example, the use of bioptic telescopes by drivers who are visually impaired has been advocated by some vision specialists but considered hazardous by others (65–67). Among those who favor them, the assumption is that these devices will be used according to the instructions provided by the manufacturer and the eye care specialist prescribing them. Although there is evidence that drivers use them mostly to spot signs (65–67), they will experience inattention blindness as they switch their fixation from the carrier lens to the bioptic. A talking global position system might be a safer option for older drivers with visual impairments. Adaptive cruise control, lane alert warnings, and self-parking cars may also be a boon to drivers with visual impairments, but studies are yet to be forthcoming on these issues.

**Aging**

Driving accidents and convictions are higher in youths and in the elderly (2,68–77), but there are large individual differences. No consistent factors, such as cognitive decision making, attention, driving experience, or training programs, have been identified.

**Stereopsis**

Investigations of stereopsis and driving performance (78–80) have failed to disclose any important impact of reduced function.

**TRADITIONAL VISION TESTING**

**Visual Acuity**

Visual acuity has traditionally been evaluated by reading a series of progressively smaller letters or symbols on a chart. For the most part, this procedure has been shown to be effective in providing a quick, accurate, and easily
administered test that is relevant to the driving task. The methodology for visual acuity assessment has been standardized, and it is unlikely that meaningful improvements to the procedure will be achieved through more extensive research. This procedure therefore appears to be adequate for vision screening for a driving license.

**Contrast Sensitivity**

Contrast sensitivity is measured in many different ways with no consensus as to which method is most appropriate for driving. At the present time, contrast sensitivity is regarded as an important visual factor for driving, but the use of a specific screening procedure has not yet been achieved. Moreover, a determination of the amount and quality of information that it can provide beyond visual acuity needs further investigation.

**Visual Fields**

Visual field testing is time consuming. Rapid screening techniques such as the Humphrey matrix have been able to generate a screening procedure that takes 20–30 seconds per eye in those without defects and 60 seconds per eye in those with defects. However, this procedure only evaluates the central 30° radius of the visual field, thereby limiting its utility for evaluation of the full visual field. There are a number of other rapid screening techniques, but they have not been subjected to a rigorous investigation in this setting.

**CURRENT ISSUES IN VISION AND DRIVING**

As of 2004, all drivers licensed in Florida who are 80 years and older are required to meet a minimum visual acuity requirement to renew their driver licenses. They are required to pass a letter acuity test of 20/40 or better at the time of renewal or provide a certificate from a licensed allopathic physician, osteopathic physician, or optometrist demonstrating that they have passed a vision test within the past year. When comparing prelaw and postlaw periods, the all-cause fatality rate, adjusted for age, race, and sex, among all aged drivers increased by 6% but decreased by 17% among drivers aged 80 years and older (88). Prior research done by Shipp and others (89–93) had suggested that states with mandated visual acuity tests have lower motor vehicle collision fatality rates among older individuals. Grabowski et al (88) found that in-person license renewal was related to a significantly lower fatality rate among the most elderly drivers. More stringent state licensure policies related to vision or road tests and more frequent license renewal cycles were not independently associated with additional benefits. After controlling for middle-aged daytime driver deaths, the only policy related to significantly lower driving fatality rates was the requirement for in-person license renewal. License renewal included a visual acuity test or a referral to a medical practitioner for further medical screening in some states.

**PHYSICIAN REPORTING OF VISUALLY IMPAIRED DRIVERS**

Physicians working in jurisdictions where reporting a patient who is at high risk for a motor vehicle accident is not mandatory still have a moral and ethical obligation to report in order to preserve patient and public safety (83,84). The Duty to Warn is a legal rationale intended to provide means of protecting the patient from an unreasonable risk of harm. Failure to warn patients of conditions that create a risk of injury will be upheld as a cause of action against eye care providers when it can be shown that the failure to warn is the proximate cause of an injury. Patients may argue that they had insufficient warning of their impairment, and because of their impairment, their operation of a motor vehicle or other machinery resulted in an injury. Thus, patients whose vision no longer legally qualifies them to operate a motor vehicle should be warned not to drive and a notation to this effect should be entered into the patient’s record (86,87).

In 1999, the American Medical Association (AMA) House of Delegates approved a recommendation that calls on doctors to breach patient confidentiality for the good of both the patient and the society. The AMA stated that it is desirable and ethical for physicians to notify the Department of Motor Vehicles or an equivalent agency if an impaired patient fails to restrict driving appropriately (87).

Mandatory reporting concerns include the question of relative benefit, and different states have varying legal opinions about mandatory reporting. If mandatory reporting detours someone from confiding or getting necessary care, because he or she fears losing driving privileges, then reporting statutes could backfire, creating more hazardous drivers. There has been a long-standing controversy as to whether driving is a privilege or a right. Driving is subject to reasonable regulations in the interest of public safety and welfare. The suspension or revocation of an operator’s license is not intended as a punishment to the driver but is designed solely for the protection of the public. The AMA Physician’s Plan for Older Drivers’ Safety (2003) (3) states that every physician (we would include optometrists) should assess risk factors for older patients who drive (4). For those individuals at risk of unsafe driving, the practitioner should recommend a formal assessment of vision, cognition, and motor skills and also refer for a road test when appropriate.

**ANTICIPATED FUTURE DEVELOPMENTS**

The UFOV is a specialized visual field test that has been developed for evaluation of driving and peripheral vision (32–37). It differs from other tests of peripheral visual function by incorporating measures of reaction time, stimulus localization, simultaneous central and peripheral visual tasks (multitasking), target identification, and complex decision making. The UFOV provides a means of
evaluating the driver’s ability to perform multiple tasks accurately and quickly to simulate the driving task. Studies performed with this procedure indicate that it correlates with driving performance (32–37). This procedure is now being used by a greater number of health care professionals who are concerned with driving and other mobility tasks; but careful research has been limited to only a few laboratories, and there is a strong need for additional work. Currently, the UOVO test is considered too costly and time consuming to be used for screening on a widespread population basis.

The rapid increase in vision and driving research has generated a number of questions as to the impact on safe driving of multisensory integration of information and assimilation of sensory, cognitive, decision making, and attentional properties. Also, important are validation of laboratory studies when applied to population implementation and public policy, rehabilitation and training regimens to compensate for disabilities, evidence-based guidelines, and legal liabilities. No single group is capable of addressing all relevant issues, and a consolidation of this information through meta-analysis or overviews can sometimes be difficult. The Cochrane Report (69) provides a comprehensive objective assessment of current findings and directed efforts primarily toward identifying the importance of vision screening for prediction of traffic accidents and fatalities. The authors concluded that 1) no studies to date met their inclusion criteria (randomized controlled trial before and after studies comparing vision screening to nonscreening of drivers aged 55 and older), 2) there is insufficient evidence to assess the effect of vision screening on elderly drivers, and 3) valid and reliable vision screening tools need to be developed to properly evaluate this topic in a more thorough fashion.

CONCLUSIONS

Our knowledge concerning the relationship between visual performance and driving has increased in recent years. Highly competent laboratories and research teams have conducted a number of research studies and evaluations. However, policy decisions, accuracy and efficiency of testing large populations, interpretation of test results, legal ramifications, and risk assessment currently determine the requirements for a driving license. A procedure that is highly effective in a research project has not yet been found applicable for general use in screening drivers.

The United Kingdom and other countries have adopted a uniform vision standard for driving licensure. The United States has not, with the result that there are 50 standards of visual performance needed to obtain a driving license. There are also meaningful variations in the licensing requirements among different countries in Europe, Asia, and South America. We propose that the United States adopt a national vision standard for driving personal vehicles similar to that of the United Kingdom. Such a standard would place the responsibility on drivers rather than eye care providers to know if they are visually qualified to drive, and enforcement would be conducted by departments of motor vehicles and law enforcement agencies. This approach would also remove concerns about mandatory reporting of impaired drivers by health care professionals. It would be an application of the principle used in qualifying for a commercial driving license.

REFERENCES


87. Foubister V. To tell or not—physician’s reports on patients driving impaired. American Medical News. November 22, 1999:8.
89. Levy DT, Vernick JS, Howard KA. Relationship between driver’s license renewal policies and fatal crashes involving drivers 70 years or older. JAMA. 1995;274:1026–1030.
Vision and Driving: Canada
Payam Yazdan-Ashoori, BMSc, Martin ten Hove, MD

Abstract: Supported by the findings of a major review of vision standards for driving in Canada, the Canadian Ophthalmological Society’s Committee on Vision Standards for Driving issued a series of recommendations in 2000 to the Canadian Medical Association. Many of these recommendations, including changes in visual acuity and visual field standards and consideration for exceptional cases, have been implemented across Canada. Canadian courts have stated that it is important to provide on-road assessments for visually impaired individuals who wish to continue driving. Most Canadian provinces and territories will allow visually impaired drivers a license if they pass the test. However, these on-road assessments use scarce resources and may be expensive for the driver. Limited licensure is a widespread practice, but whether it effectively protects drivers is not established. Except for Alberta, Quebec, and Nova Scotia, all Canadian provinces and territories have legislated mandatory reporting of visually impaired drivers by vision care providers.

doi: 10.1097/WNO.0b013e3181dfa982
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The recently published Canadian Vehicle Survey shows that in 2008, Canadian drivers logged more than 294 billion vehicle-kilometers in vehicles up to 4.5 tons (1). Considering that 74% of Canadians aged 16 and older own a motor vehicle, this translates to an average of 16,000 kilometers driven per driver (2).

Such a high level of vehicular travel creates the potential for motor vehicle accidents. The Canadian Council of Motor Transport Administrator’s (CCMTA) Mid-Term Review of its Road Safety Vision 2010 (3) initiative showed that serious injuries due to motor vehicle accidents in Canada decreased more slowly than desired. Between 2002 and 2005, driving fatalities decreased but have now increased back to 2002 levels. In terms of fatalities per vehicle-kilometers traveled, Canada performs poorly when compared to other Organization for Economic Development and Cooperation (OECD) member countries, ranking only 11th of 30 nations.

The CCMTA is focused on 7 major traffic safety issues: speed, unbelted occupants, drinking drivers, commercial vehicles, vulnerable road users, intersections, and rural roads (2). Although the causes of most motor vehicle crashes are multifactorial and complex, medical fitness and adequate vision are recognized as essential prerequisites for drivers to operate motor vehicles safely. Specific data linking driving accidents to vision are lacking. However, it can be argued that impaired vision may be a contributory cause of accidents involving at least 4 of the 7 aforementioned traffic safety issues, including commercial vehicles, vulnerable road users, intersections, and rural roads. Moreover, the prevalence of impaired vision among Canadians in their driving years is significant. More than 4 million Canadians suffer from age-related ocular conditions, including macular degeneration, glaucoma, diabetic retinopathy, and cataract (4). In 2006, 278,000 Canadians had a visual acuity between 20/40 and 20/200; 108,000 were legally blind. These figures are projected to double over the next 25 years (4). Setting an appropriate minimum vision standard for driver licensure is therefore critical to the safety of our society.

In 2000, Casson and Racette (5) reviewed vision standards for driving in Canada, which helped the Canadian Ophthalmological Society’s Committee on Vision Standards for Driving to form its recommendations to the Canadian Medical Association (CMA) and CCMTA (6). Many of these recommendations, including changes in visual acuity and visual field standards and consideration for exceptional cases, have been implemented across Canada and published in the CMA’s Determining Medical Fitness, seventh edition (7).

This review will outline the current visual standards in each of the Canadian provinces and territories for private drivers and include the newly implemented functional assessments being used to evaluate exceptional cases. The current literature on vision and driving is discussed and graded.

In preparing this report, we reviewed all official ministry Web sites as well as links to acts and regulations of the respective provinces and territories for relevant information on vision standard policies to obtain a class 5 driving license.
(Private drivers are called class G in Ontario and class 5 in all other provinces and territories.)

Because some information is not available online or in print, we contacted appropriate representatives from each jurisdiction directly by telephone and interviewed them. Questions focused on vision standards for driving, functional assessments, restricted licensing, and mandatory reporting. We interviewed medical professionals in each jurisdiction, including physicians and occupational therapists, to determine which specific tests were used in clinical evaluations. Finally, the current literature on vision and driving was reviewed and graded. We searched relevant databases, including Ovid MEDLINE, AARP AgeLine, and CINAHL with an emphasis on literature published after 2000. Appropriate limits were applied, and Medical Subject Heading terms were used. Following the Canadian Task Force system of grading evidence (8), we assigned numbers from highest to lowest levels of evidence by study design (Table 1).

VISION STANDARDS FOR DRIVING IN CANADA

The CCMTA publishes medical standards for drivers (9) that are largely derived from the CMA’s Guidelines for Physicians: Determining Medical Fitness to Operate Motor Vehicles (7). Although each province and territory determines its own visual standards, most adopt the standards published by the CCMTA and all participate in the development of the standards through their active membership in the CCMTA.

Most of the existing literature on vision and driving fails to provide high-grade evidence on which to base visual performance standards for safe driving. Because most studies employ outcome measures of vehicular crash or serious injury, it would be unethical to conduct a randomized control trial involving drivers with naturally occurring visual impairments. Therefore, the majority of studies are descriptive or observational in nature, ranging from evidence level 2 to 5. A 2009 Cochrane review (10) failed to find any level 1 studies on vision screening in older drivers and motor vehicle crashes. Studies on vision and driving are frequently contradictory. For instance, the implementation of minimal vision requirements in the United States for older drivers attempting to renew their licenses was found in one study to reduce crash fatalities (11) but not in another (12).

Given that our present standards and guidelines are based on the current literature and expert opinion, it is not surprising that there are varying views on whether they are well founded. After searching through more than 1,500 publications, Molnar et al (13) concluded that published guidelines for determining medical fitness to drive were not evidence based. Beran (14) concluded that Australia’s guidelines were not supported by published studies. The following is an overview of visual standards used or under consideration for use in Canada.

Visual Acuity

The corrected visual acuity requirement for obtaining a class 5 driving license in most Canadian jurisdictions is a Snellen equivalent 20/50 with both eyes open. New Brunswick and Nova Scotia require a minimum of 20/40 in the better eye. Studies examining the relationship between visual acuity and driving performance reach conflicting conclusions. Some older studies suggest that poor visual acuity is linked to a greater number of accidents. Hofstetter (15) found that drivers with binocular visual acuity in the lowest quartile experienced an increased number of crashes in a study that involved 13,786 drivers over a 12-month period. A similar analysis of 1,000 British drivers aged 55 years or older found that a binocular visual acuity of 20/30 or better distinguished accident-free drivers from accident-involved drivers (16). In contrast, Fonda (17) found that a visual acuity of 20/200 was sufficient to recognize 6 specified traffic signals at a safe enough distance to allow for early stopping at 40 miles per hour. A 5-year retrospective cohort study of all Florida drivers aged at least 80 years, published in 2008 (18), found lower rates of motor vehicle collisions after a visual acuity standard was implemented for license renewals and extensions.

In the United Kingdom, visual acuity screening for drivers is measured by reading a number plate like that fixed to a motor vehicle with letters and numbers geometrically equivalent to a Snellen visual acuity of 20/50 (19). Individuals must be able to read this number plate from a distance of 20.5 m (letters and numbers, 79 mm high and 57 mm wide). A 2003 study (20) showed that only 92.3% of 210 individuals with a corrected visual acuity between 20/30 and 20/40 could read all number plates correctly, suggesting that this visual acuity standard is more difficult to meet than that of Canada. A similar study (21) showed that 26% of 50 patients with a visual acuity of 20/30 failed and 35% of 50 patients with a visual acuity of 20/40 passed the plate test, further demonstrating the poor correlation between Snellen visual acuity and success on the number plate reading test. This discrepancy may occur because of the crowding effect (22), the reduced probability of correctly identifying optotypes when letters and numbers are combined, or the variation in letter acuity of different fonts (23). Another study (24) found that letter acuity is a function of the complexity of the font, stroke width, and letter height. This finding becomes especially pertinent because as of September 1, 2001, drivers in the United Kingdom must be able to pass the test when viewing from a distance of 20 m, a newer font of letters and numbers 79 mm high but only 50 mm wide.

Visual Fields

Visual field requirements are consistent throughout Canada in that most jurisdictions adhere to the CCMTA recommendation of unimpaired vision within an area of 120
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<td>Bilateral cataract surgery improves contrast sensitivity and driving performance</td>
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<td>McBride and Matson (46)</td>
<td>An aspherical intraocular lens results in faster simulated breaking response times than spherical lenses</td>
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<td>Szlyk et al (48)</td>
<td>Glaucoma patients with poorer contrast sensitivity have poorer simulated driving performance</td>
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<td>Drivers with impaired contrast sensitivity have later breaking times and faster approaches at intersections</td>
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<td>UFOV</td>
<td>Ball et al (52)</td>
<td>A poor UFOV predicts crashes with high sensitivity and specificity</td>
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<td>Owsley et al (53,54)</td>
<td>Older drivers have reduced UFOV and increased crash risk and injurious accident involvement</td>
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<td>Ackerman et al (55)</td>
<td>Impaired UFOV in elderly is a risk factor for driving cessation</td>
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<td>Fisk et al (56,57)</td>
<td>Stroke and traumatic brain injury survivors have impaired UFOV</td>
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<td>Clay et al (58)</td>
<td>Poor UFOV in elderly is associated with unsafe and negative driving performance</td>
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*1, meta-analysis or randomized controlled trial; 2, prospective or retrospective cohort; 3, case-control; 4, case series or cross-sectional study; 5, expert opinion. UFOV, Useful Field of View test.
There are no restrictions on class 5 licensure for monocular vision. Monocular vision testing remains elusive. In studying the impact of field defects on driving in 10,000 California drivers, Johnson and Keltner (25) found that those with binocular field loss had accident and traffic conviction rates twice that of individuals with no losses. In studying motor vehicle accident rates among patients with glaucoma, McGwin et al (26) found a greater risk among those with moderate (odds ratio [OR] = 3.6 with 95% confidence interval [CI], 1.4–9.4) or severe (OR = 4.4 with 95% CI, 1.6–12.4) visual field deficits in the central 24° than in those with no defects. A study of the use of driving simulators in 40 patients with glaucoma (27) found that a visual field less than 100° along the horizontal meridian was associated with an almost 3 times greater level of simulated accidents compared to age-matched control subjects without field loss. However, a small prospective cohort study involving 9 patients with cerebral field defects including homonymous hemianopia (28) found no differences as compared to a control group of 10 individuals without a history of cerebral injury in driving simulator performance as measured by speed, reaction time, or driving error rate.

Cause and effect relationships are difficult to establish with respect to visual field loss and driving. In an Australian study of 100 senior drivers (29), investigators determined that an expanse of 120° along the horizontal meridian was defined by a stereoacuity of greater than 200 seconds) and 10° above and below the horizontal meridian is a poor predictor of on-road driving performance. The European Commission recommends a visual field standard of 120° along the horizontal meridian as well as a binocular visual acuity of 20/40 for its member states (30). These standards were implemented in a study involving 100 individuals with central and/or peripheral visual field defects who underwent a standard driving test conducted by the Dutch driving license authority. The standards had a sensitivity of only 0.79 and specificity of only 0.48 for predicting practical fitness to drive based on a standard checklist administered by a driving examiner (31).

Based on this evidence, the characteristics of visual field loss that make motor vehicular operation unsafe remain unknown, and therefore, a valid standard for visual field testing remains elusive.

**Monocular Vision**

There are no restrictions on class 5 licensure for monocularly sighted individuals in Canada. The CMA Driving Fitness document states that monocular vision limits depth perception. However, it recognizes that monocular cues, such as relative size, texture, interposition, and parallax, may help individuals with no binocular stereopsis. Currently, every jurisdiction allows monocular driving. The CMA and the CCMTA recommend that drivers who suddenly become monocular refrain from driving for an adjustment period of several months, with implementation of the adjustment period and its duration left to the physician.

Published evidence supports the current policies of permitting unrestricted driving for individuals with adequate vision in one eye only. In the study by Johnson and Keltner (25), drivers with monocular visual field loss had accident and traffic conviction rates comparable to those of age-matched control subjects. McKnight et al (32) reported similar driving abilities among 40 monocular and 40 binocular truck drivers. In a 1994 study (33), 1,400 male drivers from Quebec who were involved in accidents during their 70th year were compared to subjects who were not involved in accidents during their 70th year. The binocular status and visual acuity of each driver were known. The risk of accidents was equal in drivers who were monocular (as defined by a stereoscopic view of greater than 200 seconds) and those who were binocular at acuities of 6/12 to 6/15. Edwards and Schachat (34) reported that self-reported driving ability was unaffected in 71 patients who had one eye enucleated. Racette and Casson (35) found on-road performance to be unaffected in monocular drivers regardless of the side of the affected eye.

**Diplopia**

Diplopia within the central 40° of the visual field is not tolerated for any driver class unless it is corrected by obscuring one eye or using prisms while maintaining the requirements for visual acuity and fields.

In 2001, White et al (36) compared 10 Saskatchewan drivers with stable diplopia of various causes to 10 age-matched control subjects on driving simulator cue recognition involving braking, accelerating, and steering, as well as threat-recognition performance. The outcome variables were reaction times and missed responses. The diplopic drivers performed as well as the control subjects. The degree of misalignment, duration of diplopia, presence or absence of diplopia in primary position, and presence or absence of compensatory head position did not alter performance. Age was the only significant predictor of driving performance in both groups.

**Color Vision**

No driving standards are in place regarding color vision in Canada. The CMA and CCMTA agree that drivers must be able to distinguish traffic light colors. The CMA and CCMTA recommend that drivers be made aware of color deficiencies by their physicians.
Studies investigating the role of color vision in driving have shown a possible effect on driving ability. Atchison et al (37) found that error rates and response times were worse in 49 color-deficient men than in 20 men with normal vision asked to identify a red or yellow stimulus. Another laboratory study (38) found that as compared to color-normal subjects, deuteranopes were less able to detect red, orange, and green (but not yellow or blue) road traffic signs projected for 300 milliseconds. Therefore, the color coding of signs and signals has a potential effect on driving performance. Another study (39) discovered that when a sunglass tint was similar to the stimulus color, response times and errors were poorer in color-deficient individuals than that in normal control subjects. A questionnaire study (40) comparing color-normal subjects to 151 individuals with color deficiencies found that the color-deficient individuals had relatively greater difficulty in detecting road reflectors and rear signal lights of preceding cars ahead at night than during the day. The importance of adequately recognizing brake and traffic lights prompted Australia to preclude protanopes from obtaining a commercial driving license in 1994 (41).

Owing to a paucity of evidence and improvements in hue and intensity of red signal lights, current Australian medical standards for drivers allow licensure for any color vision defect (42).

**Contrast Sensitivity**

There are several methods by which contrast can be measured, and there is no consensus on a gold standard. Moreover, the measurement of contrast sensitivity is rarely performed by ophthalmologists except in research studies. Experts acknowledge that impaired contrast sensitivity may affect driving, but no rules govern this issue as it is still unclear what level of reduction poses a risk (7). The CMA and CCMTA recommend that physicians inform their patients of a deficit in contrast sensitivity.

Although there is no driving standard involving contrast sensitivity, studies have shown that poor contrast sensitivity may affect driving performance. Owlsley et al (43) found that older drivers with cataract were 2.5 times more likely to have had at-fault motor vehicle accidents in the past 5 years than those without cataract. A subsequent study by Owlsley et al (44) found this difference to be attributable to impaired contrast sensitivity even when the lens opacity was in one eye only. In another study (45), driving performance was measured in 29 patients who had undergone bilateral cataract surgery after a period of at least 1 month (mean of 80 days). In a closed-road circuit, driving scores were found to be significantly improved from preoperative levels and similar to scores of 18 normally sighted control subjects. Logistical regression analysis determined that contrast sensitivity was the main determinant of the difference.

Improvement in contrast sensitivity after cataract surgery was explored further in a double-masked study using a driving simulator under night vision conditions (46). Patients who had undergone cataract surgery with an aspherical intraocular lens had braking response times 0.5 seconds faster than those with a spherical lens. Driving at 55 miles per hour, drivers with an implanted aspheric lens would detect highway signs and pedestrians 45 feet earlier. Driving simulators were also used to determine a relationship between contrast sensitivity and driving. Patients with glaucoma with lower contrast sensitivity, as determined by Pelli-Robson letter contrast sensitivity charts (47), drove in a simulator at slower speeds, had more lane boundary crossings, and had longer braking response times despite normal visual acuity with mild to moderate visual field loss (48). On-road driving performance was also poorer. Those with impaired Pelli-Robson contrast sensitivity made inappropriately fast approaches at intersections and tended to initiate braking too late (49).

**FUNCTIONAL ASSESSMENTS**

In 2004, the CMA guidelines added a section on functional (on-road driving) assessment to the present visual standards in order to allow those with reduced visual function to demonstrate that they could drive safely. This modification resulted from a 1999 Supreme Court decision in British Columbia (50) in which a man with stroke-induced homonymous hemianopia was repeatedly denied a class 5 driving license based on his failing to meet the 120° visual field standard. The Supreme Court determined that the blanket refusal to issue a driving license was unjustified and that individuals have the right to a valid assessment of their driving abilities. Another pertinent judicial precedent was set in a case involving a commercial driving license (51). A man with binocular acuity of 20/70 owing to congenital optic atrophy had earned a living as a truck driver for 13 years until his visual impairment became known, at which time his driving license was revoked despite a good driving record and favorable opinions from several ophthalmologists. The court reinstated his driving privileges after he successfully passed a functional assessment at the province’s expense and awarded him lost wages.

As a result of these judicial rulings, Canadian provinces and territories allow functional assessments in some cases. For example, Ontario permits them only for those who fail to meet the 120° horizontal visual field standard. However, all other jurisdictions permit them even for those who fail the visual acuity standard. For example, Saskatchewan will allow a functional assessment for individuals with binocular visual acuity between 20/50 and 20/60. In other smaller jurisdictions, the decision of whether or not to perform a functional assessment is physician driven. The level of driving license eligible for a functional assessment varies as well. In Ontario, only private class 5 (or G) drivers may be eligible, whereas in Manitoba, all classes are eligible.

A vision waiver pilot program was implemented in Ontario in May 2005 whereby drivers have the ability to obtain a license despite failing to meet the visual field...
requirement. Such drivers must successfully complete a clinical assessment by an occupational therapist and an on-road driving test. The clinical assessment involves measurements of physical strength, range of motion, visual perception through the Motor-Free Visual Perception Test, visual attention as measured by the Useul Field of View test (UFOV), visual scanning through the Brain Injury Visual Assessment Battery for Adults (bIVABA scan course), and an interview to determine the individual’s level of insight and awareness of visual limitations. The on-road assessment consists of 2 road tests designed to assess target maneuvers and the use of strategies to compensate for the visual field impairment.

Other Canadian provinces and territories have not formalized their vision waiver process but do use similar assessments. In most instances, the functional assessment is conducted by an occupational therapist. Referrals for a functional assessment may come from a physician, the relevant provincial licensing authority, an insurance company, a family member, or even the patient. An occupational therapist chooses a battery of tests and schedules a road test conducted by a driving evaluator and an occupational therapist. The functional assessment report is sent to the provincial licensing authority where the final decision is made based on the functional assessment and reports from eye care providers.

Since 1978, Quebec has had a statute to allow drivers with a medical disability to prove their ability to drive safely. But functional assessments began only in 2004, consisting of a predefined circuit road test conducted at any of the 41 service centers. Implementation has increased at a rate of 15% per year. Among 750 license suspensions each year based on medical reasons, approximately 70% involve visual problems, mostly visual field defects. Many of these suspensions result from an eye examination required at the age of 75 years. Nearly 50% of individuals whose driving license has been suspended for these reasons request a functional assessment. About 97% of these patients pass the functional assessment and are granted a driving license. This pass rate is appreciably higher than the approximately 50% pass rate of functional road assessments from all medical causes in Quebec and the 65% pass rate of Ontario’s Vision Waiver Program (Dr. Jamie Dow, MD, oral communication, August 14, 2009).

A recent unpublished study by Dr. Jamie Dow of the Société de l’Assurance Automobile du Québec prospectively conducted road assessments from January 1, 2009 to April 30, 2009, on 109 visually impaired individuals with visual field defects. Of these, 91 successfully passed the test. He found that the only significant predictor of driving performance was age; everyone younger than 60 years passed. Neither the type nor the degree of visual field defect was predictive of driving performance.

These results are in agreement with data from Ontario’s Vision Waiver Program. As of September 2010, 755 individuals have successfully obtained a driving license. Among the 403 individuals who did not pass, more failures resulted from poor performance on the clinical testing than on the road test. Licenses were not granted to 55 individuals; only 17 failed the road assessment. The other 38 failures were due to the elements in the vision waiver program that Quebec omits, namely, clinical occupational therapy assessments (Angela Litrenta, Driver Improvement Office, Ministry of Transportation, Ontario, oral communication, September 10, 2009). Data have not been widely available on the number of functional assessments that have been conducted, pass rates, and subsequent accidents, violations, or withdrawals.

**USEFUL FIELD OF VIEW TEST**

An emerging tool in vision and driving research is the UFOV. This test is incorporated into many functional assessment protocols because it is easy to administer and is a valid and repeatable measure of visual attention. The rationale behind measuring visual attention is that visual fields do not capture the complexity of visual information that the driver must process concurrently from both central and peripheral fields.

The UFOV test has 3 components, each scored from 0 to 30, a higher score indicating poorer performance. The processing speed is assessed by measuring the average time required to correctly identify a series of centrally presented stimuli. Divided attention is tested by identifying a simultaneously presented central and peripheral stimulus. Selective attention is measured in the same way. To perform well, the subject must ignore distracting stimuli added to the viewed panorama. Scores are summed to obtain an overall UFOV score.

Ball et al (52) discovered that a deficient UFOV predicted motor vehicle crashes with 89% sensitivity and 81% specificity. Owsley et al (53) later found a reduced UFOV in older drivers with increased accident risk (54) and traffic accidents that produced injuries. In drivers older than 60 years, poor UFOV was associated with environmental scanning difficulties and positioning difficulties (cognitive tunnel vision) (49). Ackerman et al (55) found that an impaired UFOV was a contributory risk factor for driving cessation in the elderly. Fisk et al (56) discovered a poor UFOV in 50 stroke (57) and 23 traumatic brain injury survivors. A cumulative meta-analysis by Clay et al (58) showed that a poor UFOV was associated with unsafe driving in the elderly.

Such studies suggest that UFOV may be a good predictor of driving performance. In a recent study of 1,801 older drivers (59), glare sensitivity, visual field loss, and UFOV were all predictive of motor vehicle crashes, whereas visual acuity, contrast sensitivity, and stereoaucity were not.

Because it is difficult to find a single visual measure that can independently predict performance on the road, the road test has a valid role. Drivers who suffer from age-related macular degeneration, glaucoma, and retinitis pigmentosa learn to employ compensatory strategies. For instance, one study found that reducing speed for central field defects and increasing scanning for peripheral field defects were deemed effective strategies in a driving simulator and on the road (60).
Therefore, an individualized road assessment (35) and a battery of clinical tests including UFOV may combine to form a powerful predictor of traffic safety and the motivation behind functional assessments for exceptional cases.

RESTRICTED LICENSURE

Functional assessments may lead to unrestricted or restricted driving licensure. Restricted licenses may permit driving only in daylight, within a given area, on 2-lane highways, with automatic transmissions, or with speed restrictions. With the exception of Ontario, every Canadian province and territory offers restricted licenses. Inter-provincial interchangeability may be an issue.

Marshall et al (61) found that restricted licensure significantly decreased the number of crashes and traffic violations in Saskatchewan. In Manitoba, speed and daytime restrictions are placed automatically if visual acuity falls to 20/60 binocularly. For the restrictions to be removed, the individual must successfully undergo functional assessment.

MANDATORY REPORTING

Mandatory reporting of drivers deemed unfit by physicians is not universal in Canada. With the exception of Alberta, Quebec, and Nova Scotia, all provinces and territories have legislated mandatory reporting by physicians with protection against legal liability. In Nova Scotia, optometrists must mandatorily report. In Alberta, the patient must self-report. Where physician reporting is discretionary, as in Alberta, Quebec, and Nova Scotia, physicians are protected against legal liability. In British Columbia, where the physician must report a driver who continues to drive after being warned, protection from legal liability is limited to those circumstances. All reports must be mailed or faxed in writing, usually on a letterhead or predefined form to the appropriate provincial or territorial office.

CONCLUSIONS

The vision standards for driving in Canada continue to follow the recommendations of the CCMTA and CMA. Although it has been shown that problems with sight can be a major reason why individuals restrict themselves from driving (61), courts have stated that it is important to provide assessments for individuals who wish to continue driving. Ontario limits these assessments to the private class driving license and only for visual field deficits, whereas other provinces and territories will consider a waiver for any visual deficit in more than 1 class of driving license.

Functional assessment is an evolving concept that currently involves clinical assessment performed by an occupational therapist followed by a road test. In Quebec, only the road test is necessary. Two obvious concerns with functional assessments include the lack of standardization, especially with regard to the clinical tests, and the growing demand on scarce resources. For example, in the province of Newfoundland and Labrador, drivers are assessed by a single occupational therapist. Many jurisdictions have only 1 or 2 institutions where functional assessments can take place, making it difficult for individuals who are not near major centers. Although the costs of functional assessment may be offset by government subsidy, most assessment centers charge substantial fees for their services. Finally, the data collection process necessary to analyze the driving records of those currently driving as a result of a functional assessment is not well defined, making it difficult to determine whether these practices are effective in ensuring public safety.

REFERENCES

14. Beran RG. Analysis and overview of the guidelines for assessing fitness to drive for commercial and


Section Overviews

Lanning B. Kline, MD

To be successful, the Journal of Neuro-Ophthalmology must meet and hopefully exceed the expectations of its readership. First and foremost, the journal is committed to publish original research, both basic and clinical. Next, given the nature of our subspecialty, unusual cases with important teaching points allow us to constantly evaluate our diagnostic acumen and clinical practice. Finally, reviews highlighting evolving concepts in neuro-ophthalmic disorders, discussions of controversial topics affecting evaluation and treatment of our patients, and the importance of clinical-pathological correlation in better understanding disease mechanisms are all subjects of great interest to our readers. Meeting these expectations will be accomplished through a number of regular sections that will appear in the journal. Organized by leaders in neuro-ophthalmology, section editors outline below their objectives in keeping the readership current in dealing with the challenges encountered in neuro-ophthalmology.

Photo Essay

Timothy J. McCulley, MD

The Photo Essay section is designed primarily for the presentation of clinical cases that are best represented in pictures. This includes cases with unique imaging findings or ones in which a few good photos are all that is needed to tell the story. Although photo essays lend themselves to descriptive studies, they do not necessarily have to be so limited case reports. Smaller investigational contributions in which pictures are the main measure would make welcome additions. For example, findings of newly developed imaging techniques applied to neuro-ophthalmic disorders would be welcome.

State-of-the-Art Review

Randy H. Kardon, MD, PhD, Grant T. Liu, MD

The purpose of the State-of-the-Art Review is to provide readers with new insight into the diagnosis, pathophysiology, and treatment of a variety of conditions that are encountered by neuro-ophthalmologists in their care for patients. These reviews will bridge the gap between what has previously been published and new findings that are shifting thinking toward a new conceptual framework of specific disorders. New findings will include diagnostic techniques, pathophysiologic mechanisms, and evolving treatments. Authors who are invited to write a State-of-the-Art Review or those who would put forth an unsolicited submission should have personal research and clinical expertise in the subject area chosen, in order to present their own data in addition to highlighting relevant literature on the topic. Summary art and photographs will provide essential content for this section in order to help readers visualize the State-of-the-Art concepts being discussed.

Basic Science in Neuro-Ophthalmology

Lynn K. Gordon, MD, PhD, Jeffrey L. Bennett, MD, PhD

Basic Science in Neuro-ophthalmology is dedicated to presenting original scientific manuscripts investigating the pathophysiology of neuro-ophthalmic disorders. Submitted manuscripts should use translational or clinical scientific methods to investigate molecular, immunologic, or physiologic mechanisms of disease. Hopefully, the readership will gain a greater appreciation of the science as well as the art of our subspecialty.
Clinical-Pathological Case Study

Neil R. Miller, MD

As in other fields of medicine, clinical-pathological correlation remains an important means in understanding disease mechanisms in neuro-ophthalmology. To this end, this section will consist of cases presented in a manner similar to those that appear in the Clinical-Pathological Case (CPC) section of the New England Journal of Medicine. They will be culled from those presented at the Walsh Section of the annual meeting of the North American Neuro-Ophthalmology Society. The format will consist of an initial case presentation by the primary author, followed by comments from a neuroradiologist on diagnostic imaging studies. Further information from the primary author will follow, leading up to biopsy results, autopsy results, or both, which will be discussed by a neuropathologist. The diagnosis will then be revealed, and the primary author will discuss the salient features of the condition. We hope that the cases presented in this section will be useful to the reader not only for their general importance in our field but also for the uniqueness that made them “Walsh cases.”

Point Counter-Point

Andrew Lee, MD, Valérie Biousse, MD

The goal of the Point Counter-Point section is to provide our readers with expert discussion of controversial topics in the field of neuro-ophthalmology. We will avoid topics for which solid evidence is available and emphasize controversial issues that make the practice of neuro-ophthalmology so challenging. Upcoming topics include whether corticosteroids should be used to treat nonarteritic anterior ischemic optic neuropathy, whether positive neuromyelitis optica (NMO) antibodies should alter our management of optic neuritis, whether indirect traumatic optic neuropathies should be observed or treated, and whether new treatments for radiation optic neuropathies are truly efficacious. Readers of the journal are encouraged to let us know what they would like to be debated in the Point Counter-Point section. We welcome your comments.

Literature Commentary

Mark L. Moster, MD, Michael S. Lee, MD

Literature Commentary presents abstracts on research relevant to the field of neuro-ophthalmology. Articles reviewed are chosen from both the neurology and ophthalmology literatures. Commentary on the merit (or lack thereof) of each article and its relevance to neuro-ophthalmic practice is provided from a neurologic and ophthalmologic perspective.

Books Received

Michael S. Vaphiades, DO

Books Received is designed to provide our readership a survey of recently published texts of interest to neuro-ophthalmologists. The section will outline the contents of each book, intended audience, details on figures and photographs, and price. Hopefully, this will give the reader the necessary information to decide whether to purchase the textbook for themselves or their residents, fellows, or medical students.

Neuro-Ophthalmology News

Kathleen B. Digre, MD

Neuro-ophthalmology News will feature articles that may affect the practice of neuro-ophthalmology. It will also highlight ongoing activity of the North American Neuro-Ophthalmology Society and showcase a variety of topics including medical education, academic issues, and clinical practice. We welcome comments and suggestions to keep this section vital and informative.
Rapid Progressive Unilateral Visual Loss in an Elderly Man

Joshua Pasol, MD, Linda Sternau, MD, Patrick Luetmer, MD
Caterina Giannini, MD, PhD

Dr. Pasol:
A 75-year-old man experienced sudden loss of vision in his right eye. His past medical history was significant for non-insulin-dependent diabetes, hypertension, hypercholesterolemia, and an abdominal liposarcoma. He was receiving treatment for glaucoma with pressure-lowering drops and had been noted to have normal visual fields prior to the onset of visual loss. He denied any symptoms of temporal arteritis.

An examination at an outside facility 3 weeks after the onset of visual loss revealed vision of counting fingers in the right eye and 20/30 vision in the left eye, a right relative afferent pupillary defect, and a swollen right optic disc associated with peripapillary hemorrhages. The left eye had normal visual function with a normal fundus appearance except for a 0.6 cup-to-disc ratio. The patient was diagnosed with presumed anterior ischemic optic neuropathy (AION).

Over the next several months, the vision in the right eye deteriorated to no light perception.

The patient presented at our institution about 4 months after the onset of visual loss. At that time, his visual acuity was no light perception in the right eye and 20/25 in the left eye. Color vision with the left eye was normal using Ishihara plates. Confrontation field testing in the left eye showed a full field; automated static perimetry using a Humphrey perimeter resulted in unreliable responses. Eye movements were full. Slit-lamp biomicroscopy revealed a mild cataract in both eyes. The right optic disc was swollen superiorly and nasally, with pallor temporally. The fellow optic disc was normal (Fig. 1). Mild diabetic retinopathy was present in the periphery of both fundi.

The patient underwent an evaluation that revealed an erythrocyte sedimentation rate (ESR) of 38 mm/hr and a C-reactive protein (CRP) level of 1.72 mg/dL. Prednisone 60mg was started and an immediate biopsy of the temporal artery was performed and revealed mild atherosclerosis. Steroids were therefore discontinued. Other laboratories were either negative or normal including: ACE, RPR, ANA, ANCA, Myeloperoxidase, dsDNA, NMO IgG antibody assay, and vitamin B12 level. Neuroimaging was obtained.

Dr. Luetmer:
Magnetic resonance imaging (MRI) of the orbits reveals enhancement and mild enlargement of the right optic nerve extending from the orbit to the optic chiasm. (Figs. 2a–c).

Dr. Pasol:
A diagnosis of possible optic neuritis was made, and the patient was given a 5-day course of intravenous methylprednisolone 1000 mg without improvement. An optic nerve biopsy was recommended but declined by the patient. He was therefore examined both clinically and with neuroimaging at regular intervals over the next several months. During this time, the right eye remained blind. Repeat MRI was performed.

Dr. Luetmer:
The repeat MRI shows progression of the enhancement and an increase in the size of the optic nerve, particularly within the orbit (Figs. 3a–c).

Dr. Pasol:
Approximately 1 year after onset of visual loss, the patient underwent a biopsy of the right optic nerve via a right lateral craniotomy. At the time of surgery, the intracranial segment of the right optic nerve was noted to be enlarged and appeared grey in color (Fig. 4). Pathologic specimens were obtained and sent for further evaluation (Figures 5a–d).

Dr. Giannini:
The pathology specimen shows disorganized tissue with microcyst formation (Fig. 5a), dense fibrillary tissue and elongated spindle cells (Figs. 5b and 5c), and degenerating axons (Rosenthal fibers, Fig. 5d). The appearance is that of a typical benign pilocytic astrocytoma involving the optic nerve.

Diagnosis
Pilocytic astrocytoma (WHO grade I) of the optic nerve.

Dr. Pasol:
There are numerous causes of acute visual loss. A complete history and physical examination and, in many
cases, the course of the visual loss (i.e., progressive, stable, or improvement) are fundamental in reaching the correct diagnosis. This patient was first diagnosed with presumed anterior ischemic optic neuropathy (AION) because of the acute presentation and the ophthalmic findings of optic disc swelling with peripapillary hemorrhages. The vision, however, proceeded to deteriorate to no light perception, which is not typical of non-arteritic AION but that can occur with arteritic AION. Thus, after the ESR and CRP were found to be slightly elevated and despite the lack of constitutional symptoms typically experienced by patients with giant-cell (temporal) arteritis, the patient was placed on a short course of systemic steroids and a temporal artery biopsy was performed. Red flags were also raised when the optic disc remained swollen months after the onset of loss of vision, thus raising the suspicion of another process causing the loss of vision. The finding on MRI of enlargement and enhancement of the right optic nerve suggested an inflammatory process such as sarcoidosis or an infiltrative tumor such as a lymphoma or glioma. Accordingly, the patient was treated with a short course of high-dose steroids. When the MRI appearance of the nerve did not improve, an optic nerve biopsy was performed, revealing a low-grade pilocytic astrocytoma.

**FIG. 1.** Appearance of the optic discs. The right disc is swollen superiorly and nasally, and there is mild temporal pallor. The left optic disc is slightly small and surrounded by peripapillary atrophy.

**FIG. 2.** MRI 4 months after onset of visual loss. Fat-suppressed post-gadolinium axial (A-B) and coronal (C-E) T1 images of the orbits demonstrate uniform enhancement involving the posterior half of the right optic nerve within the orbit extending to the level chiasm. There is mild enlargement of the orbital segment of the nerve (C) with more bulbous enlargement of the nerve just central to the optic foramen (E). Note that the enhancement is confined to the optic nerve and there is no enhancement or thickening of the dura in the region of the optic canal or anterior clinoid process.
Optic nerve gliomas are rare in adults. These tumors can range from low-grade tumors as in this case to infiltrating tumors such as anaplastic astrocytoma (WHO grade III) and glioblastoma (WHO grade IV). Pilocytic astrocytomas are usually seen in children and young adults and are present in 15% to 20% of patients with neurofibromatosis type 1 (1). Wulc et al. reported seven cases of optic nerve pilocytic astrocytoma in patients ranging from 18 to 61 (2). One of their cases had NF1. Other cases have been reported in adults (3–4), but none appear to have been as old as ours. Unlike benign optic nerve gliomas, malignant optic nerve gliomas (MONGs) are most often reported in older individuals. Wabbels et al. reviewed 45 cases of MONG in the literature (12). The mean age of diagnosis was 54 with a mean survival time of just over 8 months.

The typical presentation of adult optic nerve PAs is progressive loss of vision and variable proptosis (2–4). The vision can range from 20/30 to no light perception. Most cases are associated with slowly progressive visual loss. Sudden visual loss, as seen in our patient, may occur from acute hemorrhage within the infiltrated nerve or from ischemia in the region of maximum compression. Sudden visual loss can also occur in patients with other types of optic nerve tumors such as optic nerve sheath meningioma (5) and malignant optic nerve gliomas (6). Other ocular findings in both children and adults with optic nerve PAs include an ipsilateral relative afferent pupillary defect, optic disc swelling or pallor, peripapillary hemorrhages, and retinochoroidal (shunt) vessels (2).

The diagnosis of a PA is based on a combination of clinical findings, neuroimaging, and, ultimately, pathologic findings. The pathology is characteristic of a low-grade astrocytoma (WHO grade I), including spindle-shaped (hair-like) cells, a fibrillary background (see Figs. 5a-c), degenerating axons (Rosenthal fibers; see Fig. 5d), eosinophilic granular bodies, and, in some cases, areas of cystic...
degeneration (7). Mitotic figures and necrosis are absent, thus differentiating these tumors from higher grade gliomas, although the cellular proliferation rate as evidenced by the Ki67 index, is somewhat variable. Although some authors consider these tumors to be “hamartomas,” they are, in fact, true tumors and should be considered as such with respect to assessment and management.

Both computed tomographic (CT) scanning and MRI can detect these tumors. Both typically reveal enlargement and enhancement of the nerve; however, of the two, MRI is the study of choice due to its ability to delineate the extent of involvement. CT is useful to evaluate the size of the optic canal and to assess the presence of neural calcification that might be associated with an optic nerve sheath meningioma. In our case, the initial MRI 4 months after symptom onset demonstrated uniform high T2 signal and uniform enhancement confined to the optic nerve with mild associated mass effect. The imaging differential diagnosis of this

**FIG. 5.** A. Photomicrograph showing disorganized tissue with microcyst formation (arrows). H&E 10X. B. Photomicrograph with dense fibrillary tissue and elongated spindle cells (arrows). H&E 20X. C. Photomicrograph showing the classic fibrillary background and elongated spindle cells (pilocytic) indicated by arrows. 40X H&E. D. Photomicrograph revealing several Rosenthal fibers (pink elongated structures indicated by arrows). 100X H&E.
appearance includes both inflammatory and neoplastic conditions. Sarcoidosis and, rarely, tuberculosis and syphilis can present with this picture. Wegener granulomatosis also can involve the optic nerve, but rarely in isolation. Within the neoplastic category, lymphoma can present as an isolated optic neuropathy with this imaging appearance (11). In our patient, a meningioma could be excluded based on the imaging appearance, as meningiomas typically demonstrate low T2 signal and a “tram-track” or “doughnut” enhancement of the optic nerve sheath with no enhancement of the nerve.

The management of optic nerve pilocytic astrocytomas is somewhat controversial. For children, most authors recommend observation alone with radiation therapy, chemotherapy, or surgical resection used in cases of progressive visual loss not due to amblyopia, an increase in the size of the tumor by neuroimaging, or disfiguring proptosis. The number of cases of PAs reported in adults is too small to warrant a definitive recommendation; however, the cases reported suggest that the visual and systemic prognoses generally are good, and thus are similar to the prognoses in children. Thus, treatment is used when necessary to protect the fellow eye from being affected by extension of the tumor to the optic chiasm and, hopefully, improve vision in the affected eye. Radiation, chemotherapy or surgery may be used in selected cases (8). In adults more than children, careful monitoring by clinical examination and neuroimaging is essential to identify the rare cases of malignant transformation that can be occur spontaneously or following radiation (9,10,13). It has been recommended that our patient receive radiation to protect the vision in his fellow eye from chiasmal involvement.

REFERENCES
Should Steroids be Offered to Patients With Nonarteritic Anterior Ischemic Optic Neuropathy?

Andrew G. Lee, MD, Valérie Biousse, MD

The treatment of nonarteritic anterior optic neuropathy (NAION) remains very limited and disappointing. Recent publications have suggested that oral steroids as well as intravitreal injections of steroids might be helpful to accelerate resolution of disc edema and improve visual outcome. However, the use of steroids to treat acute NAION remains largely debated.

PRO—Steroids should be offered to patients with nonarteritic anterior ischemic optic neuropathy: Andrew G. Lee, MD

Opening Statement:
It remains an inconvenient truth that to date, there is no proven effective therapy for nonarteritic anterior ischemic optic neuropathy (NAION). This situation is frustrating for both the patient and the clinician. Although clinicians make recommendations for improving the general health of the patient and treating any vasculopathic risk factors (e.g., blood glucose, cholesterol, blood pressure, diet, exercise, tobacco cessation, and sleep apnea), the lack of an effective therapy for NAION remains a major issue for neuro-ophthalmologists. A number of older and more recent reports (1–5) have suggested that systemic corticosteroids might be useful in NAION. Much speculation in the past and more recently has surrounded the potential mechanisms for steroids in NAION, including reduction of vascular permeability, cell membrane stabilization, reduction of edema, and even neuroprotection. Indeed, many physicians are currently offering steroids to patients as a treatment option for NAION (6).

The pro-con debate in this issue of the Journal of Neuro-ophthalmology is not designed to answer the question or provide a standard of care. Instead, it is meant to be thought provoking and promote dialogue among neuro-ophthalmologists on an important subject. Valerie Biousse, MD, and I will debate this issue in a Point-Counter-Point format and will review and summarize the relevant literature.

Over the past 4 decades, a variety of reports have documented various routes of administration for steroid therapy for NAION. These include intravenous (6), peribulbar (7), retrobulbar (2,7), and, most recently, intravitreal (8–10). However, these studies are all anecdotal and yielded only limited and unconvincing data.

Sohan Hayreh, MD, an acknowledged expert in the field, has devoted a great deal of time and effort in his career to the study of NAION. Two prior studies had looked at the use of systemic steroids for NAION using very small numbers of patients. Foulds (1) reported improvement in visual acuity in 11 of 13 patients (85%) treated with systemic corticosteroids (60 mg prednisone daily), compared to 5 of 11 patients (45%) not treated with systemic corticosteroids. Hayreh (3) noted improvement in visual acuity in 6 of 8 patients (75%) treated with steroids (40–60 mg prednisone daily combined with initial dose of 40 units ACTH) compared to 2 (25%) in which vision either stabilized or deteriorated.

A prospective, randomized, controlled study with masked outcome assessment (Class 1 evidence) would be the best means to answer the question of efficacy of steroids in NAION. However, prior attempts by Hayreh and others have been unsuccessful in securing funding for such a study. In 2007, Hayreh (4) reported on 591 consecutive patients (749 eyes) with NAION. From clinical data available, 237 eyes with NAION were started on steroid therapy within 2 weeks of onset and 343 eyes did not receive treatment. The protocol for steroid therapy called for an initial dosage of 80 mg of prednisone daily. After 2 weeks, tapering down of therapy was started in steps of 5 days each to 70 mg, 60 mg, and then cutting down by 5 mg every 5 days to 40 mg until the optic disc edema was no longer present. The prednisone was then rapidly tapered and discontinued. Most patients were on treatment for approximately 2 months. Results of this study demonstrated that when steroid therapy was begun within 2 weeks of onset of NAION, the median time for optic disc edema resolution was 6.8 weeks, compared to 8.2 weeks in untreated cases ($P < 0.0001$).

In 2008, Hayreh and Zimmerman (5) reported a patient choice study that included 613 consecutive patients (696...
eyes) with NAION. Of the patient cohort, 312 patients (364 eyes) voluntarily opted for systemic corticosteroid therapy and 301 (332 eyes) chose no treatment. Of the 312 patients who opted for steroid therapy, 236 received treatment within 2 weeks of onset. At the initial visit, all study patients underwent detailed ophthalmic evaluation. Snellen visual acuity and Goldmann perimetry were performed on all patients, and improvement in visual function was the primary outcome measure. The treatment group received 80 mg oral prednisone daily for 2 weeks followed by a tapering dose (70 mg for 5 days, 60 mg for 5 days, and 5 mg reductions thereafter every 5 days). The median follow-up was 3.8 years. At 6 months from the onset of the NAION, eyes with an initial visual acuity of 20/70 or worse and seen within 2 weeks of onset in the treated group had a visual acuity improvement in 69.8% (95% confidence interval (CI): 57.3%–79.9%). This was in contrast to the control group of untreated patients who had a 40.5% (95% CI: 29.2%–52.9%) visual improvement. The odds ratio of improvement was 3.39 (95% CI: 1.62–7.11; \( P = 0.001 \)).

Likewise, for visual field improvement at 6 months from onset of NAION, in the treated group for those seen within 2 weeks of onset with moderate to severe initial visual field defect, there was improvement in 40.1% (95% CI: 33.1%–47.5%) compared with 24.5% (95% CI: 17.7%–32.9%) in the untreated group. The odds ratio for visual field improvement was 2.06% (95% CI: 1.24–3.40; \( P = 0.005 \)). Hayreh concluded that NAION treated during the acute phase with systemic corticosteroids resulted in a significantly higher probability of improvement in visual acuity (\( P = 0.001 \)) and visual field (\( P = 0.005 \)) than in the untreated group.

I believe that this evidence cannot be completely ignored and that patients deserve the opportunity to hear about the results of this study in an objective manner from a trusted source. In my own practice, I explain to patients the results of the Hayreh studies and the controversial components. We review the difference between a patient choice method-ology (such as Dr. Hayreh’s work) and a randomized, prospective, controlled clinical trial. I believe that the published reports by Hayreh are useful for generating a hypothesis, but I acknowledge that for hypothesis testing, a randomized clinical trial is necessary. One of the worst things that can happen to a patient with an untreatable disease like NAION is for the physician to say, “Nothing can be done.” Admittedly, I am operating in a less than optimal and, in some cases, data free zone for many of my current therapeutic recommendations, but much of medicine remains outside the realm of Class I evidence. In addition, I acknowledge that corticosteroids have significant systemic side effects in elderly and patients with vasculopathy for whom steroids might worsen many systemic disorders including hypertension and diabetes.

I tend to steer patients away from steroids if they have minimal or mild visual loss from their NAION, severe or brittle diabetes or hypertension, active infections, or significant peptic ulcer disease history. On the other hand, for patients with 20/70 or worse visual acuity who I see within 2 weeks of onset of NAION and who do not have significant risk for steroid-related side effects, I do offer them the opportunity to choose or decline steroid treatment. Inevitably, patients who are told that nothing can be done will find the long list of purported therapies for NAION including the steroid literature. I would much prefer them to ask me questions and receive an informed opinion rather than getting all of their information from the Internet. I do not offer steroids to patients with 20/70 or better vision, who have risks for steroid use, or who are greater than 2 weeks out from the event. I am also more likely to offer steroid treatment in 3 clinical settings: patients with optic disc edema from NAION in whom no visual loss has occurred (incipient NAION), patients with monocular vision, or the uncommon patient with bilateral simultaneous NAION.

Finally, we might be dismissive of steroid therapy for NAION since this form of treatment has not been efficacious in ischemic events of the central nervous systems such as stroke. However, it is still unproven that ischemia due to arterial insufficiency is the cause of NAION. Inflammatory, mechanical, and venous etiologies have all been postulated for NAION and, with any of these mechanisms, steroids may play a beneficial role.

In summary, I believe until a randomized clinical trial is performed, the decision for steroids in NAION should be an individual one that is made by the patient and not by the doctor. In my opinion, the role of the physician is to treat vasculopathic risk factors of the patient, provide information for an informed decision, and act as a trusted source of therapeutic decision making in a controversial area.

### CON—Steroids should not be offered to patients with nonarteritic anterior ischemic optic neuropathy: Valérie Biousse, MD

**Opening Statement:**

Although numerous practitioners recommend steroids to treat nonarteritic anterior ischemic optic neuropathy (NAION) (7), this practice is not based on any Class I evidence and is potentially dangerous (6). Not being able to offer treatment to patients with potentially blinding disorders is very difficult and frustrating, and it takes much longer to make a patient with NAION understand why no treatment is a reasonable option than to write a prescription for steroids. This might explain why
approximately 10% of physicians reported treating NAION with oral steroids and 19% of neurologists chose high-dose intravenous steroids in a recent survey (6). Since this survey was conducted, a large case series proposing oral steroids within 2 weeks of onset of NAION was published (5), followed by a few case reports suggesting that intravitreal injections of steroids might also be used to treat NAION (8–10). These reports leave room for debate as to whether patients with NAION should receive steroids or not.

Because the pathophysiology of NAION remains elusive, it is difficult to propose informed hypotheses regarding treatment of NAION (7,11). Small vessel circulatory insufficiency of the optic nerve head is the most widely accepted pathophysiology of NAION, but the mechanism of ischemia remains uncertain (11–15). The optic nerve head is supplied by an anastomotic arterial circle (derived from the short posterior ciliary arteries) with distinct upper and lower halves, consistent with the altitudinal defects often seen in NAION (16). Fluorescein angiography studies provide the most compelling indirect evidence that circulatory insufficiency in the paraoptic branches of the short posterior ciliary arteries is the primary cause of NAION; however, no adequate systematic histopathologic studies of these vessels have been performed, and it is not known whether there is associated atherosclerotic change or thrombosis (12). Levin and Danesh-Meyer (15) even recently proposed that NAION may primarily be a venous disease; however, this theory remains speculative.

A number of well-designed studies in the neurologic literature have shown that steroids do not improve the outcome of patients with acute arterial or venous cerebral ischemia (17,18). Indeed, it has even been suggested that steroids can be detrimental to patients with acute cerebral ischemia and should not be prescribed (17,18). The same concerns may apply to NAION, which is a presumed vascular disorder, most often occurring in older patients who have vascular risk factors (19–21).

Initially widely used in acute cerebral injuries to reduce cerebral edema, steroids are currently limited to treating cerebral edema associated with brain tumors and bacterial meningitis. Over the past decade, studies have shown that the efficacy of steroids in acute spinal cord injury is limited and that steroids should not be prescribed to patients with acute traumatic brain injury or traumatic optic neuropathies (22). Although steroids are commonly used in numerous ocular disorders, including selected ocular vascular disorders, it is important to emphasize that the main purpose of the steroids in various ocular vascular disorders is to reduce retinal edema, a major cause of visual loss in diabetic retinopathy and retinal vein occlusion (23). Although a recent study utilizing optical coherence tomography (OCT) demonstrated that 8 of 76 patients with NAION examined within 4 weeks of visual loss had subfoveal fluid, likely responsible for some of the reversible visual loss (24), and the primary cause of irreversible visual loss in NAION is direct damage to the optic nerve (11). Administration of steroids to reduce macular edema does not seem necessary in most cases of NAION.

Patients with a small cup to disc ratio are predisposed to NAION and are said to have a disc at risk (4,25,26). It has been suggested that swelling within the confines of a tight disc may produce a compartment syndrome (4). The crowded axons swell in the restricted space, and capillaries and other small vessels among the nerve fibers are compressed, resulting in cytotoxic and vasogenic edema that worsens infarction and tissue loss. A number of medical and surgical interventions have been proposed to shorten the duration of disc edema, presumably to stop this vicious circle and treat the compartment syndrome (7,11).

Optic disc edema is by definition present in NAION and characteristically persists a few weeks (4,11). A recent study showed that the median time (25th–75th percentile) to spontaneous resolution of optic disc edema from onset of visual loss was 7.9 (5.8–11.4) weeks (4). Resolution time was longer in patients with diabetes than in patients without diabetes (P = 0.003), and multifactor analysis showed that worse initial visual field defects (P < 0.0001) and acuity (P = 0.04) were associated with faster resolution (4). There is, however, no evidence that decreasing the duration of disc edema improves visual outcome.

Interestingly, the rationale for the use of steroids in NAION comes from a study from the late 1960s that postulated that steroids would decrease capillary permeability, thereby inducing faster resolution of disc edema (1). This, in turn, would reduce compression of capillaries in the optic nerve head and improve blood flow, restoring the function of surviving but nonfunctioning ischemic axons. In that study (1), improvement in visual acuity occurred in 11 of 13 patients (85%) treated with systemic steroids (60 mg prednisone daily), compared to 5 of 11 patients (45%) not treated with systemic steroids. In 1974, Hayreh (3) reported improvement in visual acuity in 75% of 8 treated NAION eyes, compared to 17% of 6 untreated eyes. Neither study was randomized, and it is difficult to draw conclusions from so few subjects. There have been no studies using high-dose intravenous steroids in NAION and no randomized controlled studies investigating the role of oral or intravitreal corticosteroid therapy (7). The current controversy was triggered by a recent report by Hayreh and Zimmerman (5) supporting the use of oral steroids to treat acute NAION and a few anecdotal reports of patients with NAION treated with intravitreal injections of triamcinolone (8–10,27–29).

The recent large study by Hayreh and Zimmerman (5) suggested that oral prednisone might improve the visual fields and visual acuity of patients with NAION. In this nonrandomized study, patients self-selected their treatment and the examiner was not blinded to treatment. Despite the large number of patients, these 2 major causes of bias severely limit the validity of the study. In those patients treated with steroid therapy within 2 weeks, the median time to optic disc edema resolution was 6.8 weeks, compared to


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Dr. Biousse nicely outlines the con side of the controversy. I have no problem with the facts that she elucidated, namely, that there is no Class 1 evidence (i.e., randomized controlled clinical trial) for the use of steroids in NAION. The absence of proof of efficacy however is not the same as proof of the absence of efficacy. I readily acknowledge that there is a junk yard in medicine littered with treatments, touted as effective anecdotal for multiple conditions, which are only later found to be ineffective or even harmful. Nevertheless, many treatments that have been proven to be effective in a large randomized clinical trial had their humble start in anecdotal case reports, case series, or observational cohorts.

The idea that reduction of macular edema might be one mechanism for the improvement in NAION after steroids is intriguing, and high-resolution OCT might show that intravitreal triamcinolone has the advantage of fewer systemic side effects, it may result in persistent increased intraocular pressure that may worsen optic nerve damage. Since this first report, 5 others reported that patients with NAION (4 from Turkey (9) and 1 from Korea (10)) have received 4 mg intravitreal triamcinolone acetonide, 4–10 days after visual loss. All patients experienced some visual improvement and the authors suggested that triamcinolone improved disc edema (9,10). However, a previous report from Germany (28) described 3 patients treated with a much higher dose (20 mg) of intravitreal triamcinolone within 1 week of visual loss. One eye developed triamcinolone-induced ocular hypertension, and visual acuity did not improve in these patients.

NAION remains frustrating for clinicians and often devastating for patients. The pathophysiology remains uncertain, and it is uncertain whether any treatment will be effective for NAION (7). The role of steroids remains controversial, and although steroids (particularly intravitreal steroids) might accelerate resolution of disc edema, there is currently no evidence that a shorter duration of disc edema is associated with improved visual outcome (29); additionally, the benefits of steroids on possible associated macular edema are probably very limited clinically. Results of recent studies need to be interpreted carefully, and controversy should be seen as stimulus to expand our research on the pathophysiology and treatment of NAION rather than as proof that steroids are an effective treatment for acute NAION (29).

I do not currently recommend the use of steroids (intravenous, oral, or intravitreal) to treat NAION, and I limit their use to those cases with arteritic anterior ischemic optic neuropathy.
Rebuttal: Valérie Biousse, MD

Dr. Lee acknowledges being in a “data free zone” when treating patients with NAION. The history of medicine is filled with examples of treatments administered to thousands of patients without strong evidence, that later turned out not only to be ineffective, but also harmful. Optic nerve sheath decompression for NAION (30), corticosteroids for traumatic optic neuropathy and traumatic brain injury (22), oral steroids for acute optic neuritis (31), systematic anticoagulation for cerebral ischemia (17), and indiscriminate carotid endarterectomy (17) are only a handful of these examples. I never tell a patient that “there is nothing to do” and I carefully weigh treatment options. However I do not prescribe a treatment based on a patient’s request. Indeed, one of the roles of physicians is to decide what treatments should or should not be offered to patients, most of whom do not have the experience or training to make such decisions. It is because we as physicians have such an enormous responsibility, that we need to be as rigorous as possible in our recommendations. Modern medicine is about evidence, which remains weak in NAION.

Summary: Lanning B. Kline, MD

This Point Counter-Point highlights 2 issues that have proven very frustrating for clinicians in dealing with patients with NAION: 1) the underlying pathophysiology of NAION remains unknown, and 2) we have less than optimal data dealing with the treatment of this optic neuropathy.

Drs. Lee and Biousse have clearly addressed the pros and cons sides of the use of corticosteroids in patients with NAION. They have outlined the 2 conundrums listed above yet realize that the practice of medicine is often imperfect. Much to his credit, Sohan Hayreh, MD, has gathered, in a meticulous fashion, a tremendous amount of clinical data on the natural course of NAION in both patients untreated and those given systemic steroids. Lacking a prospective, randomized, double-masked clinical trial, the results of Hayreh’s studies provide the best data we have. As physicians, we do not want to deprive our patients of any treatments that may lead to improved visual function, yet at the same time, we strive to practice evidence-based medicine and use caution in prescribing corticosteroids, a treatment with significant potential side effects.

I hope you enjoyed reading this new format of Point Counter-Point. I look forward to filling the pages of Letters to the Editor with your comments. Please join in the discussion of this important yet controversial topic!

REFERENCES


Background: Ischemic optic neuropathy is the most common cause of perioperative vision loss. The authors sought to determine its incidence and identify risk factors that may contribute to perioperative ischemic optic neuropathy associated with nonophthalmologic surgical procedures at their institution.

Methods: Seventeen patients who experienced perioperative ischemic optic neuropathy were included in a retrospective chart review case-control study. The authors matched each patient with 2 control patients who had a similar surgical procedure but did not lose vision. They analyzed multiple perioperative variables for the case and control groups.

Results: From among 126,666 surgical procedures performed during the study period, the authors identified 17 patients with perioperative ischemic optic neuropathy, yielding an overall incidence of 0.013%. There were no hemodynamic variables that differed significantly between the patients with ischemic optic neuropathy and the matched control patients.

Conclusion: The authors conclude that perioperative ischemic optic neuropathy can occur in the absence of atypical fluctuations in hemodynamic variables during the perioperative period.

This study suffers from its retrospective nature, but there are no prospective studies of perioperative visual loss of which I am aware. I think this is the best article thus far on this topic. The most commonly cited article on this subject is by Myers et al (1). Their study found that a lot of blood loss and a long operative time were associated with ischemic optic neuropathy (ION). However, the study was poorly performed using scattered information from previously published cases and data from colleagues. The controls came from Myers’ institution.

In the current study by Holy, all the hemodynamic variables (preoperative, intraoperative, and postoperative) were available for all cases and controls. The controls came from the same institution as cases with similar operative dates. The authors show that patients with perioperative ION lose blood, experience anemia and hypotension, and undergo long surgical procedures, but these and numerous other variables do not differ from controls without visual loss.

Obviously, this does not help understand the pathophysiology or why this happens to some individuals and not others. However, it supports the idea that no single factor appears to initiate the event.

—Michael S. Lee, MD


Michael, I agree that this is an important article. The strength of this retrospective case study is that all patients were at a single institution and all examined by the same neuro-ophthalmologist. It teaches us that the risk of ION after coronary artery bypass graft (CABG) and spine surgery is approximately 1 in 300 and that with other surgeries, it is much rarer—approximately 1 in 33,000.

The findings will modify the way I counsel patients with perioperative ION. In the past, if I was able to review the hospital record and see that mean arterial blood pressure dropped to 56, hematocrit dropped to 26, or the patient received intraoperative transfusion, I would likely explain that these were the causes. Even though they still might contribute to ION, what I did not realize prior to this report is that the control patients had very similar hemodynamic changes and that these changes are likely the norm for CABG and spine surgery, rather than the exception.

The authors suggest that a larger study might have found an association of perioperative nonarteritic anterior ischemic optic neuropathy (NAION) with a disc at risk. I also think that they have made the criteria of a disc at risk too liberal, using a cup-to-disc ratio of 0.2 or less. I would contend that most of our patients with NAION have a more crowded cup-to-disc ratio of 0.1 or less, and perhaps, using such a definition, this study might have found an association.

Another finding in this study was that 16 of 17 patients were men. This likely is significant, but the design of the study—where the 2 controls for every patient were matched by gender—would preclude the ability to find statistical significance.

—Mark L. Moster, MD

Another consideration about this retrospective study is that the data may not truly be accurate. An anesthesiologist doing...
a case may see the blood pressure drop to 60/30 mm Hg for 5 minutes may not record the drop for fear of litigation. I think it probably happens, but the question is, “how often?”

I do not think that anyone could answer this, but we have to take the data at face value. Of course, that type of inaccurate reporting could happen just as often with or without ION.

—Michael S. Lee, MD


Background: Perioperative visual loss (POVL) accompanying nonocular surgery is a rare and potentially devastating complication but its frequency in commonly performed inpatient surgery is not well defined. We used the nationwide inpatient sample to estimate the rate of POVL in the United States among the 8 most common nonocular surgeries.

Methods: More than 5.6 million patients in the nationwide inpatient sample who underwent principal procedures of knee arthroplasty, cholecystectomy, hip/femur surgical treatment, spinal fusion, appendectomy, colorectal resection, laminectomy without fusion, coronary artery bypass grafting, and cardiac valve procedures from 1996 to 2005 were included. Rates of POVL, defined as any discharge with an International Classification of Diseases, Ninth Revision, Clinical Modification code of ischemic optic neuropathy (ION), cortical blindness (CB), or retinal vascular occlusion (RVO), were estimated. Potential risk factors were assessed by univariate and multivariable analyses.

Results: Cardiac and spinal fusion surgery had the highest rates of POVL. The national estimate in cardiac surgery was 8.64 per 10,000 and 3.09 per 10,000 in spinal fusion. By contrast, POVL after appendectomy was 0.12 per 10,000. Those undergoing cardiac surgery, spinal fusion, and orthopedic surgery had a significantly increased risk of developing ION, RVO, or CB. Patients younger than 18 years had the highest risk for POVL because of higher risk for CB, whereas those older than 50 years were at greater risk of developing ION and RVO. Other significant positive predictors for some diagnoses of POVL were male gender, Charlson comorbidity index, anemia, and blood transfusion. There was no increased risk associated with hospital surgical volume. During the 10 years from 1996 to 2005, there was an overall decrease in POVL in the procedures we studied.

Conclusions: The results confirm the clinical suspicion that the risk of POVL is higher in cardiac and spine fusion surgery and show for the first time a higher risk of this complication in patients undergoing lower extremity joint replacement surgery. The prevalence of POVL in the 8 most commonly performed surgical operations in the United States has decreased between 1996 and 2005. Increased odds of POVL with male gender and comorbidity index indicate that some risk factors for POVL may not presently be modifiable. The conclusions of this study are limited by factors affecting data accuracy, such as lack of data on the intraoperative course and inability to confirm the diagnostic coding of any of the discharges in the database.

This study suffers even more than the Holy article from its retrospective nature. There are no detailed perioperative data for these patients. Additionally, the vision loss may have been preexisting or preoperative, but this is not ascertainable from the discharge diagnostic codes alone. But...where else can you find 5.6 million surgical discharges?

5.6 million surgeries give us a good sense of the national prevalence of POVL—9 per 10,000 for cardiac surgery and 3 per 10,000 for spinal fusion. Although the authors comment on predictors of POVL such as male gender and comorbidity index, these are very difficult to assess in the absence of individual details. One unexpected finding was that patients under 18 years were most apt to lose vision in this study. I cannot imagine that this is a real finding. I do not see how children are any more at risk for cortical vision loss after surgery than adults. My guess is that this is a statistical anomaly.

—Michael S. Lee, MD


Purpose: To evaluate if optical coherence tomography (OCT), by providing an objective measure of the retinal nerve fiber layer (RNFL) thickness, offers a reliable prediction of visual outcome.

Design: Prospective cohort study

Methods: Thirty-seven eyes of 19 consecutive patients from a single hospital suffering from pituitary adenomas compressing the anterior visual pathways were included and compared with 46 eyes of 23 controls. Exclusion criteria included any previous treatment of pituitary adenoma and high myopia. Seventeen patients underwent transsphenoidal surgery, and 2 patients with macroprolactinomas received dopamine agonists. Automated visual fields (VF) and OCT (fast-RNFL program) were performed before treatment and 2 weeks and 3 months after treatment.

Results: Among the eyes with a VF defect before treatment, the odds of complete recovery after 3 months from the initial VF defect was multiplied by 1.29 for each in-
crease by 1 μm of mean RNFL (odds ratio [OR], 1.29; \( P = 0.037 \)). This was independent from age and duration of symptoms, which carried their own prognostic value. Inferior RNFL was a very strong prognostic factor; OR, 6.31 per micrometer (\( P = 0.0000 \)).

**Conclusion:** RNFL thinning measured by OCT puts the patient at decreased chance of recovery of an initial VF defect 3 months after treatment in pituitary adenomas compressing the anterior visual pathways. Further studies will establish how useful this tool is for long-term visual outcome.

I am always a bit skeptical when reading yet another article describing GDx, HRT, or OCT in a new clinical situation. However, this article contributes to a change in how I practice. It is an important study that adds to a growing literature demonstrating that OCT can predict visual outcome in patients with chiasmal compression. Until recently, when a patient would ask about their visual prognosis, I might base my answer on the degree of optic pallor, qualifying any prognostic statements with “It’s really hard to predict.” I would say, “Our goal is to preserve what vision you have and anything that recovers beyond that is icing on the cake.” Now, we have a tool, which really does demonstrate axonal loss and should be more predictive. Future studies should not only predict full recovery but also what degree of recovery might be expected based on RNFL thickness.

—Mark L. Moster, MD

While OCT is being reported for just about “everything that ails you,” this one looks like it is very helpful in preoperative counseling for pituitary adenomas. The authors left out minimum signal strength (SS) as an inclusionary or exclusionary factor for the OCT’s. The SS varies from 0 to 10 and represents an indicator of scan quality. The RNFL can vary greatly depending on the SS (1), and most studies recommend using a minimum SS of at least 7–8. I think a patient should have a SS of at least 7 to be helpful in predicting postoperative outcome.

—Michael S. Lee, MD


**Objective:** To compare the efficacy, tolerability, and safety of intravenous (IV) methylprednisolone (IV MP) vs oral methylprednisolone (oMP) at equivalent high doses in patients with multiple sclerosis (MS) experiencing a recent relapse.

**Methods:** Patients with a clinical relapse within the past 2 weeks and at least 1 gadolinium (Gd)-enhancing lesion on a screening brain MRI scan were included. Forty patients with MS were randomized to receive either 1 g per day for 5 days of oMP (20 patients) or 1 g per day for 5 days of IV MP (20 patients). Expanded Disability Status Scale (EDSS) and brain MRI (dual echo and postcontrast T1 scans) were assessed at baseline and at weeks 1 and 4. The study primary research question (end point) was to compare the efficacy of the 2 treatment routes in reducing the number of Gd-enhancing lesions after 1 week from treatment initiation. Secondary outcomes were safety, tolerability, and clinical efficacy profiles of the 2 routes of administration.

**Results:** The 2 groups showed a reduction of Gd-enhancing lesions over time (\( P = 0.002 \) for oMP and \( P = 0.001 \) for IV MP) with a noninferiority effect between the 2 routes of administration at week 1. Both groups showed an improvement of EDSS over time (\( P < 0.001 \)) without between-group difference at week 4. Both treatments were well tolerated, and adverse events were minimal and occurred similarly in the 2 treatment arms.

**Conclusions:** Oral methylprednisolone (oMP) is as effective as IV methylprednisolone in reducing Gd-enhancing lesions in patients with MS soon after an acute relapse with similar clinical, safety, and tolerability profiles. This study provides class III evidence that 1 g oMP × 5 days is not inferior to 1 g IV MP × 5 days in reducing the number of Gd-enhancing lesions over a period of 1 week (mean difference in lesion reduction comparing IV MP to oMP is −20% and 95% confidence interval is −48% to +5%).

Martinelli et al performed a study powered to determine whether 1 gm per day of oral methylprednisolone for 5 days has less of an effect than the same dose administered intravenously in patients with an MS exacerbation. Their primary outcome measured the reduction in gadolinium-enhancing lesions. They found a similar reduction in gadolinium-enhancing lesions with both treatments. There was an improvement of EDSS somewhat more rapidly in the IV group, but at 4 weeks, the results were equivalent. This small study provides evidence of similarity of intravenous and oral steroids in equivalent doses for the treatment of MS exacerbation. However, for neuro-opthalmologists, it does not answer the question raised by the Optic Neuritis Treatment Trial (where a lower dose of oral steroids was associated with more frequent optic neuritis recurrence) of whether the route of administration or the dose is most linked to the increased frequency of recurrence.

—Mark L. Moster, MD

It would be great if we could translate the results of this study to other diseases we treat like giant cell arteritis, neuromyelitis optica, and severe thyroid eye disease. From what I can tell, 1 gram of oral and 1 gram of IV MP have not been studied head to head in these disorders. Hayreh did not find a difference in final outcome among patients with arteritic anterior ischemic optic neuropathy when treated with IV MP.
or high-dose oral prednisone (1). The European Group on Graves Orbitopathy showed that pulsed IV MP was better tolerated and more efficacious than daily oral prednisone for thyroid eye disease (2). Aktañan et al treated patients with moderately severe thyroid eye disease with either 1) IV MP 500 mg once a week for 6 weeks followed by 250 mg a week for 6 weeks or 2) oMP was given daily starting at 72 mg tapering every 2 weeks by 8 mg for a total of 12 weeks of treatment (3). They showed that the IV MP group achieved better outcomes. It would be of great value to demonstrate the noninferiority of 1 gram of oMP since it is easier for the doctor and the patient to go oral instead of intravenous.

As far as optic neuritis is concerned, Sellebjerø et al (4) randomized patients to oMP 500 mg daily for 5 days or oral placebo. They found rapid improvement in the oMP group with no effect on recovery. These patients were treated with symptoms less than 4 weeks, which is longer than the window of the Optic Neuritis Treatment Trial (less than 8 days). So, bottom line, 1 gram of oMP is not ready for prime time for our common neuro-ophthalmologic disorders from an evidenced-based point of view.

—Michael S. Lee, MD


Postconcussion syndrome (PCS) can affect up to 20%–30% of patients with mild closed head injury (mCHI), comprising incomplete recovery and debilitating persistence of postconcussional symptoms. Eye movements relate closely to the functional integrity of the injured brain, and eye movement function is impaired post acutely in mCHI. Here, we examined whether patients with PCS continue to show disparities in eye movement function at 3–5 months following mCHI compared with patients with good recovery. We hypothesized that eye movements might provide sensitive and objective functional markers of ongoing cerebral impairment in PCS. We compared 36 PCS participants (adapted World Health Organization guidelines) and 36 individually matched controls (i.e., patients with mCHI of similar injury severity but good recovery) on reflexive anti- and self-paced saccades, memory-guided sequences, and smooth pursuit. All completed neuropsychological testing and health status questionnaires. Mean time post injury was 140 days in the PCS group and 163 days in the control group. The PCS group performed worse on antisaccades, self-paced saccades, memory-guided sequences, and smooth pursuit, suggesting problems in response inhibition, short-term spatial memory, motor-sequence programming, visuo-spatial processing and visual attention. This poorer oculomotor performance included several measures beyond conscious control, indicating that subcortical functionality in the PCS group was poorer than expected after mCHI. The PCS group had poorer neuropsychological function (memory, complex attention, and executive function). Analysis of covariance showed oculomotor differences to be practically unaffected by group disparities in depression and estimated intellectual ability. Compared with neuropsychological tests, eye movements were more likely to be markedly impaired in PCS cases with high symptom load. Poorer eye movement function and particularly poorer subcortical oculomotor function correlated more with postconcussive symptom load and problems on activities of daily living while poorer neuropsychological function exhibited slightly better correlations with measures of mental health. Our findings that eye movement function in PCS does not follow the normal recovery path of eye movements after mCHI are indicative of ongoing cerebral impairment. While oculomotor and neuropsychological tests partially overlapped in identifying impairment, eye movements showed additional dysfunction in motor/visuospatial areas, response inhibition, visual attention, and subcortical function. Poorer subconscious oculomotor function in the PCS group supports the notion that PCS is not merely a psychological entity but also has a biological substrate. Measurement of oculomotor function may be of value in PCS cases with a high symptom load but an otherwise unremarkable assessment profile. Routine oculomotor testing should be feasible in centers with existing access to this technology.

One of the strengths of this study is that it was performed in New Zealand where there is national financial coverage for health care costs associated with head injury. There was no issue of litigation or secondary financial gain for the patients with postconcussive syndrome compared with those with no postconcussive syndrome. Additionally, by various means, the authors sorted out that the findings were not due to depression, nor were all the abnormal eye movements under voluntary control. The PCS group had poor performance on eye movement functions that were beyond conscious control including slowed velocity of self-paced saccades and longer saccade durations of self-paced saccades, antisaccades, and larger amplitude memory-guided
saccades. There were significant correlations between the self-assessed health status on various questionnaires and the abnormal ocular motor findings. The findings suggest dysfunction in prefrontal cortical areas as well as in subcortical processing. The conclusion is that the symptoms of PCS have a biologic substrate and are not purely on an emotional or voluntary level.

As neuro-ophthalmologists, we see patients after minor head trauma with many symptoms. In my practice, they are typically referred by neurologists or ophthalmologists with vague visual symptoms, including light sensitivity, photophobia, blurred vision, double vision, and headache induced by reading. The abnormal findings on ocular motor testing are reassuring to me that some of these patients are truly organic. We have a tendency, particularly in the litigious climate in the United States, to assume that these findings are either motivated by secondary gain or psychological in nature.

Eye movement recordings as done in this study are not universally available but might be considered by some of us on occasion. Perhaps, down the line, a bedside oculomotor test can be developed that can help support the organic nature of patients we see with postconcussive syndrome.

—Mark L. Moster, MD

Great! These patients really do have an organic basis to their symptoms. Interestingly, some had quantitative eye movement abnormalities with unremarkable neuropsychological testing.

However, this test may not be so clinically relevant. Even though the mean eye movement variables were significantly different between patients with postconcussive syndrome (PCS) and controls, patients with PCS fell within 2 standard deviations away from the control mean in more than 3 of 4 patients with PCS. If they had included a visual symptom as part of the inclusion criteria, I think more patients with PCS would have fallen outside this normal range.

Bottom line, it appears that oculomotor function testing could be helpful if positive, but a negative test (one that falls within 2 standard deviations of the normal mean) does not rule out PCS. A final note, we do live in a malingering prone society, and I would focus on those nonvoluntary oculomotor tests the authors describe.

—Michael S. Lee, MD


Purpose: To study the effectiveness of anti-CD20 (rituximab [RTX]; Rituxan; Genentech, Inc., South San Francisco, CA) therapy in patients with severe corticosteroid (CS)-resistant thyroid-associated ophthalmopathy (TAO).

Design: Retrospective interventional case series.

Participants: Six consecutive subjects with severe progressive TAO unresponsive to CS.

Methods: Electronic medical record review of consecutive patients receiving RTX during the past 18 months was taken. Responses to therapy were graded using standard clinical assessment and flow cytometric analysis of peripheral lymphocytes.

Main Outcome Measures: Clinical activity score (CAS), proptosis, strabismus, treatment side effects, and quantification of regulatory T cells.

Results: Six patients were studied. Systemic CS failed to alter clinical activity in all patients (mean CAS ± standard deviation, 5.3 ± 1.0 before vs. 5.5 ± 0.8 during therapy for 7.5 ± 6.4 months; P = 1.0). However, after RTX treatment, CAS improved from 5.5 ± 0.8 to 1.3 ± 0.5 at 2 months after treatment (P < 0.03) and remained quiescent in all patients (CAS, 0.7 ± 0.8; P < 0.0001) at a mean follow-up of 6.2 ± 4.5 months. Vision improved bilaterally in all 4 patients with dysthyroid optic neuropathy (DON). None of the 6 patients experienced disease relapse after RTX infusion, and proptosis remained stable (Hertel measurement, 24 ± 3.7 mm before therapy and 23.6 ± 3.7 mm after therapy; P = 0.17). The abundance of T regulatory cells, assessed in 1 patient, increased within 1 week of RTX, and remained elevated at 18 months of follow-up.

Conclusion: In progressive CS-resistant TAO, rapid and sustained resolution of orbital inflammation and DON followed treatment with RTX.

These patients were suffering from fairly severe thyroid eye disease (TED) that did not respond well to 1 mg per kg per day of oral prednisone. Four of the patients had optic neuropathy. Rituximab is indicated for rheumatoid arthritis and non-Hodgkin lymphoma. Patients receive 2 intravenous infusions separated by 2 weeks. The patients in this study showed an amazing improvement in clinical activity score, a grading system for inflammation. The natural history of TED follows Rundle curve: increasing inflammation, which leads to proptosis, ophthalmoplegia, and eyelid retraction. As the inflammation resolves over the course of 1–3 years, the proptosis and ophthalmoplegia persist. In these cases, inflammation improved dramatically over 8 weeks in most cases without improvement in Hertel measurements or strabismus. So, could this article suggest that rituximab is speeding up Rundle curve? If so, then rituximab might allow our TED patients to receive surgical treatment faster. But at what cost?

—Michael S. Lee, MD

Well, Michael, it is wonderful to have new options for treatment of TED. However, before we rush into using rituximab let us consider the following. First, this is a small case series. Second, TED tends to improve with time on its own. Third, a course of rituximab costs over $10,000. Finally, the same author that this article cites to show fewer side effects with rituximab for autoimmune disease than for...
lymphoma (1) has subsequently published a case of fatal progressive multifocal leukoencephalopathy in a patient treated for rheumatoid arthritis (2).

—Mark L. Moster, MD


Also do not forget, one patient in this study died of cardiac arrest 3 months after his last infusion. The authors do not comment that this was study related but perhaps it is.

—Michael S. Lee, MD
Progressive Optic Neuropathy in Idiopathic Intracranial Hypertension After Optic Nerve Sheath Fenestration

We read with interest the article by Wilkes and Siatkowski (1) and believe that it raises several important questions concerning the pathophysiology of papilledema. Their patient had idiopathic intracranial hypertension and underwent optic nerve sheath fenestration (ONSF) because of progressive visual loss, loss of color vision, and worsening visual field defects. The patient’s visual parameters initially improved after surgery, including the development of spontaneous venous pulsations (SVP), but visual sensory function subsequently deteriorated again despite normal-appearing optic discs and persistent SVPs, suggesting normal intracranial pressure (ICP). A ventriculoperitoneal shunt was placed without effect on progressive visual loss.

Because the subarachnoid space (SAS) of the optic nerve (ON) contains numerous trabeculae and septa (2), it is probably incorrect to consider the SAS of the ON as one continuous cerebrospinal fluid (CSF) space that allows free flow of fluid throughout. Although an ONSF appears to be able to reduce ICP (evidenced in this case by the resolution of optic disc swelling and the appearance of SVPs), it is possible that some SAS compartments still exist that contain toxic substances in the trapped CSF. In a recent study, we found a deleterious effect of lipocalin-like prostaglandin D synthase, a substance that appears to be increased in the SAS of the ON in patients with papilledema (HE Killer, MD, unpublished data), on cultured astrocytes (3). The case reported by Wilkes and Siatkowski emphasizes that the pathophysiology of papilledema may be far more complicated than we used to believe (4). The use of more sophisticated imaging techniques, such as computed tomographic cisternography, provides a dynamic view of CSF flow and ultimately may be helpful in determining the optimum treatment for patients with worsening visual function in the setting of severe papilledema.

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REFERENCES

Bisphosphonate-Induced Orbital Inflammation

We read with interest the article “Another case of bisphosphonate-induced orbital inflammation” (1). We commend the authors for a comprehensive appraisal that included detailed clinical and radiological documentation and establishment of a causal relationship between the offending drug and the clinical findings. However, we seek to refute the assertion that this case represents the first instance of orbital inflammation following bisphosphonate treatment of osteoporosis. We reported 3 menopausal middle-aged women taking alendronate (Fosamax; Merck, Whitehouse Station, NJ) for osteoporosis, 2 of whom developed manifestations consistent with orbital inflammation: myositis and posterior scleritis (2). Causal association was established similarly by the temporal relation with commencement and withdrawal of the drug.

Subsequent reports of orbital inflammation associated with various bisphosphonates administered for osteoporosis have appeared in the literature and online (3–5). Indeed,
some of these reports cite our original article. Most of these cases have responded well to drug withdrawal and systemic corticosteroid therapy. Of note, rechallenge with intravenous zoledronate produced a recurrence (3). Fraunfelder et al (6) likewise observed recurrent scleritis on rechallenge with pamidronate. We believe that this association with variants of nonspecific orbital inflammation, while uncommon, probably occurs more frequently than is recognized or reported. A variety of ocular inflammatory manifestations are present in an idiosyncratic manner with different generations and modes of administration of bisphosphonates. Since osteoporosis and autoimmune ocular diseases occur most commonly in middle-aged women, it is important that ophthalmologists are cognizant of the association of ocular and orbital inflammation with this class of drugs. Where a positive history is obtained, we urge consideration of drug withdrawal in the management plan.

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**REFERENCES**


**Response**

We thank Drs. Mbekeani and Slamovits for their interest in our article (1). As an author, one always lives in fear of receiving the news that one’s literature search did not capture all prior reports. Gunter von Noorden, MD, used to caution residents that it was unlikely that anything in the modern English medical literature was truly the first report of anything as a thorough review of the German (and other non-English language) literature would likely produce a similar prior report. We appreciate Drs. Mbekeani and Slamovits bringing our oversight to our attention (2).

We agree that ophthalmologists should always ask patients who present with orbital or ocular inflammation about the use of bisphosphonates. This is especially true in an era when many ophthalmologists may become less interested in the use of systemic medications. In obtaining a patient’s history, medication lists often look like the following: “some type of anti-inflammatory,” “some lung medicine,” “some kind of bone treatment,” or the worst shortcut of all . . . “see list.” Most of the time we get away with it as eye MDs, but what if that “anti-inflammatory” is hydroxychloroquine, that “lung medicine” ethambutol, or that “bone treatment” is a bisphosphonate?

**Bo Yang, MD**  
**Andrew G. Lee, MD**  
*Houston, Texas*

**REFERENCES**


International Neurology
Robert Lisak, MD, Daniel Truong, MD,
William Carroll, MD, and Roongroj Bhidayasiri, MD.
2009, 695 pages, Hard cover, 22 chapters
$199.95
ISBN 978-1-4051-5738-4

Referenced

Intended audience: Neurologists, neurosurgeons, and
neurology and neurosurgery fellows and residents.

Taking a unique approach to neurological illness, this
multiauthored textbook reviews the etiology, genetics, age
of onset, and clinical presentations of neurological disease
from an international perspective. There are many
neurological conditions unique to different parts of the
world, which this text highlights. For example, the chapter
on Behcet’s syndrome and the nervous system is written by
A. Siva, MD, and S. Saip, MD, both from the University of
Istanbul, Turkey, and the chapter on Takayasu’s arteritis by
Y. Kitagawa, MD, at Tokai University, Tokyo, Japan. The
text is printed on glossy paper, illustrated primarily in black-
and-white, yet with a center section of outstanding color
photographs. The book contains 22 sections including
vascular disease, autoimmune and inflammatory disease,
seizure disorders and epilepsy, the dementias, movement
disorders, other neurodegenerative diseases, infectious
diseases, demyelinating disorders, toxicology, nutritional
deficiency, peripheral neuropathies, muscle and neuromus-
cular junction disorders, neuro-otology, neuro-ophtalmol-
ogy, neuro-oncology, sleep disorders, spinal cord disorders,
CNS trauma, pain syndromes, and headache and neck/
facial pain. Within these sections, there are 173 chapters
with contributions from 219 experts from around the
world. This publication serves a definitive source of practical
information to aid in the diagnosis and treatment of
neurologic disorders.

The Study of Anosognosia
George Prigatano. 2010, 537 pages,
Hardcover
ISBN13 9780195379099
$89.95
ISBN10 0195379098

Referenced

Intended audience: Neurologists, neurosurgeons, neuro-
ophtalmologists, and neuroscientists.

This text summarizes the recent advances that have taken
place in the field of anosognosia. It reviews research findings
as the syndrome pertains to hemiplegia, Anton syndrome,
and a variety of other disorders including Alzheimer disease,
schizophrenia, and traumatic brain injury. It provides
historical references in addition to the guidelines for the
management and rehabilitation of these patients. The
figures and tables are primarily black-and-white on standard
paper except for a middle section with excellent color
images on glossy paper.

Oxford Handbook of Ophthalmology
Alastair Denniston and Philip Murray.
2009, 930 pages, Flexicover,
25 chapters
$59.95
ISBN10 0-19-955264-9

Referenced

Intended audience: Ophthalmologists, optometrists, or-
thoptists, and ophthalmic nurses and technicians.

This book is a pocket-sized synopsis of ophthalmic disease
including diagnosis and ongoing management. Chapters
include clinical skills, trauma, lids, lacrimal glands, conjunc-
tiva, cornea, sclera, lens, glaucoma, uveitis, medical retina,
orbit, neuro-ophtalmology, strabismus, and pediatric
ophthalmology. New to this edition are chapters on contact
lenses, refractive surgery, and evidence-based ophthalmology.
There is also an introduction to medical statistics as it relates
to ophthalmology. Basic perioperative care, medical emer-
gencies, and advanced life support protocols are also
included. The book’s information is easily accessed, with
areas of importance highlighted. There are 52 black-and-
white illustrations.

Neurology: A Queen Square Textbook
Charles Clarke, Robin Howard, Martin Rossor, and
Simon D. Shorvon. 2009, 991 pages, Hardcover,
25 chapters
$224.95

Referenced

Intended audience: Neurologists, neuroscientists, neuro-
surgeons, neurology, and neurosurgery fellows and residents.

This very large textbook, reminiscent of the classic texts in
neurology, is a fusion of neuroscience with traditional
neurology from one of the most prestigious international centers
of neurology. It is multiauthored and chapters include neurology
worldwide, the burden of neurological disease, nervous system
structure and function, the language of neurology, stroke
and cerebrovascular diseases, movement disorders, epilepsy,
dementia, infections of the nervous system, nerve and muscle

Books Received: J Neuro-ophtalmol 2010; 30: 207-209

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disease, multiple sclerosis and demyelinating diseases, headache, cranial nerve disorders, neuro-ophthalmology, neuro-otology, spinal cord disorders, cerebellar ataxias and related conditions, rehabilitation neurology, toxic/metabolic and physical insults to the nervous system, disorders of consciousness, intensive care neurology and sleep, neuro-oncology, psychiatry and neurology, pain, autonomic dysfunction, uro-neurology, and systemic conditions and neurology. This textbook is printed on glossy paper, with high-quality color photographs, tables, and illustrations. It is a comprehensive and authoritative reference in the field of neurology.

**Stroke Medicine (Oxford Specialist Handbooks in Neurology)**

Hugh Markus, Anthony Pereira, Geoffrey Cloud. 2010, 567 pp, Flexicover, 17 chapters

$79.95  
ISBN13: 9780199218776  
Non-referenced  
**Intended audience:** Neurologists and neurology residents.

This handbook serves as a pocket-sized practical reference source encompassing all areas of stroke. Topics range from epidemiology, neuroanatomy, vascular anatomy, history taking and examination, imaging, causes and treatment of stroke, prevention of stroke, cerebral venous thrombosis, cerebral hemorrhage, vascular dementia, recovery and rehabilitation from stroke. There are 67 black-and-white line drawings and 65 black-and-white halftones on nonglossy paper.

**Ultimate Review for the Neurology Boards: Second Edition**

Hubert H. Fernandez, MD, Stephan Eisenschenk, MD, and Michael S. Okun, MD. 2010, 600 pages, Softcover, 24 chapters

$79.95  
ISBN 1933864206/9781933864204  
Non-referenced  
**Intended audience:** Neurologists and neurology residents and fellows.

This book reviews various subjects in neurology that will appear on neurology board examination including stroke, neuromuscular disorders, infections of the CNS, epilepsy, movement disorders, demyelinating disease, clinical neurophysiology, neuro-ophthalmology and neuro-otology, neurobehavioral disorders, and psychiatry among other topics. It is written in an outline format with multiple tables and black-and-white illustrations. The book is supported by an in-depth extensive easy to navigate Web-based program with multiple color photograpgs including cases, flashcards, and a medication data bank. There is also a question and answer section with 50 practice questions.

**Controversies in Neuro-Ophthalmology: A Case Based Debate**

Andrew G. Lee, MD, Jacinthe Roleau, MD, and Reid A. Longmuir, MD. 2009, 107 pages, Hardcover, 20 chapters

$200  
ISBN 9781420070927  
**Referenced**  
**Intended audience:** Practitioners in the fields of neurology, ophthalmology, neurosurgery, and neuro-ophthalmology residents and fellows.

This multiauthored textbook book reviews controversial topics in the field of neuro-ophthalmology. It provides a comprehensive overview on clinical presentation, diagnosis, and treatment. Each of the 20 chapters opens with a case to illustrate a pertinent controversy and poses a clinical question. The questions are then discussed by leading experts in the field. Some of the controversies include:

- should a patient with unexplained isolated optic atrophy have neuroimaging and further laboratory evaluation?
- should a patient with optic disc edema and a macular star figure (neuroretinitis) have laboratory testing and treatment?
- should a young patient with a new diagnosis of optic neuritis have testing and treatment for multiple sclerosis?
- should a vasculopathic patient with NAION have any testing?
- should I treat traumatic optic neuropathy?

There are multiple black-and-white patient ocular motility and fundus photographs, visual fields, and optical coherence tomography images. Every chapter has a summary section at the end (which is of value on its own) with recommendations on how to approach each clinical controversy.

**Blueprints Neurology**

Frank W. Drislane, MD, Michael Benatar, MBChB, Bernard S. Chang, MD, Juan A Acosta, MD, Andrew Tarulli, MD, and Louis R. Caplan, MD. 2009, 219 pages, Softcover Trim Size: 8 X 10, 25 chapters

$39.95  
ISBN-10 0-7817-9685-7  
Non-referenced  
**Intended audience:** Neurologists, neurology residents, and medical students.

Serving as a review of the key topics in the field of neurology, this publication is useful for neurology board review certification and recertification tests. Its scope is very comprehensive and includes chapters on neurologic...
examination, neurologic investigations, the approach to coma and altered consciousness, neuro-ophthalmology, the approach to weakness, the sensory system, dizziness, vertigo, and syncope, ataxia and gait disorders, urinary and sexual dysfunction, headache and facial pain, aphasia and other disorders of higher cortical function, dementia, sleep disorders, vascular disease, seizures, movement disorders, head trauma, systemic and metabolic disorders, central nervous system tumors, demyelinating diseases of the central nervous system, infections of the nervous system, disorders of the spinal cord, the peripheral nervous system, disorders of the neuromuscular junction and skeletal muscle, and pediatric neurology. Each chapter has a key-points section, and there are 100 board-format questions and answers with both correct and incorrect answers. There are 54 black-and-white or monochromatic illustrations including examination techniques, neuroanatomic pathways, and neuroimaging.
Elimination of Consult Codes in Neuro-Ophthalmology: Another Blow To Our Subspecialty?

There are threats to the practice of neuro-ophthalmology from many directions. These include lack of recognition in academic centers (1), lack of reimbursement for complex neuro-ophthalmic problems (2), and lack of procedures that provide income for practitioners (3). Now we have another threat—the loss of consultation codes from the Centers for Medicare and Medicaid Services (CMS). Yet neuro-ophthalmology is a consultative subspecialty—patients do not come to us except on another physician’s request for consultation. How did this situation arise?

CMS proposed discontinuing consultation codes in July 2009. The reason for the proposal was that consultations were costing Medicare/Medicaid large amounts of money and there was evidence that consultation codes were frequently used incorrectly by physicians not knowing the difference between a referral (transferring the care from one physician to another) and a consultation (rendering an opinion about a condition and sending back to the requesting physician). In October 2009, CMS published the 2010 guidelines for payment (http://edocket.access.gpo.gov/2009/pdf/E9-26502.pdf) that eliminated this code. The rationale cited in the Federal Register was based on a review by the Office of the Inspector General entitled “Consultations in Medicare: Coding and Reimbursement” (4). CMS stated that elimination of the codes would be budget neutral as the work relative value units for new and established office visits would be increased. To quote, “We believe that the rationale for a differential payment for a consultation service is no longer supported because documentation requirements are now similar across all E/M services.” The long-term repercussion of this action is unknown. Neurology Today reported that a call to several of the private payers (Cigna, Aetna, UnitedHealthCare) revealed that they were studying whether to follow suit (5).

What is a neuro-ophthalmologist to do? Undoubtedly, we will still be called on to render opinions about complex clinical cases.

The leadership of the North American Neuro-Ophthalmology Society (NANOS) recognized that this CMS decision might have deleterious effects on the ability of neuro-ophthalmologists to maintain their income and to attract trainees. So, the organization took action. NANOS sent a letter to CMS outlining reasons that this proposal would impact our discipline and impede patients’ long-term ability to access neuro-ophthalmologists. NANOS helped to form a coalition that included societies representing endocrinology, infectious disease, rheumatology, and several neurologic subspecialties. Representing over 30,000 physicians, this coalition solicited from its members’ letters to their legislators and to CMS protesting the elimination of consultation payments. NANOS leadership participated in the Association of American Medical Colleges (AAMC) conference calls and contacted the American Medical Association. NANOS invited several other groups to participate in this coalition’s efforts, and other subspecialty societies have sounded the alarm.

NANOS surveyed its U.S. members to gather ideas on how to reduce the financial impact on their practices and engaged the services of Mr. Steven Sadowski, a principal of ECG Consultants—a well-respected national firm who frequently serves as a consultant to the AAMC. Mr. Sadowski reviewed the membership survey responses and modeled the practice economics of 7 volunteers representing different kinds of practices (surgical vs nonsurgical, neurology vs ophthalmology, academic vs private practice).

At the 2010 Annual NANOS meeting, Mr. Sadowski explained the history behind the CMS method of physician payment and focused on resource-based relative value scale with regional adjustments. From the session on “How to Earn Money in the Post-Consult World” came the following suggestions:

- “Run the numbers” of Medicare/Medicaid patients; evaluate your practice mix and what the result of this ruling will have on your practice.
- Use Medicare/Medicaid outpatient codes as new (99201-99205) or follow-up (established 99211-99215) or, where appropriate, as new or follow-up eye exams (92002, 92004, and 92012 and 92014) as we cannot use consultation codes.
- Analyze your practice for income decline and ways to improve efficiency and reduce costs.
- Find ways to maximize revenue: remember that CMS pays an extra 2% for physicians who use e-prescribing.
- If you use time codes, patient education is a factor that will be considered; documenting education time with our patients will be more important. Monitor whether...
any of your private payers have adopted this new system.

While the full impact of the CMS decision to eliminate consult codes is still uncertain, rest assured that NANOS leadership continues to serve its members by advocating for neuro-ophthalmology.

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REFERENCES


NANOS 36th Annual Meeting: Tucson, Arizona, March 7–11, 2010

The Starr Pass Marriott Resort in Tucson, Arizona, was the site of the 36th Annual Meeting of the North American Neuro-ophthalmology Society (NANOS) on March 7–11, 2010. The meeting drew a record of 393 attendees with 43 from outside of North America.

The Walsh Meeting kicked off the week, and Brian Younge, MD, and his colleagues of the Mayo Clinic were the hosts. The neuro-pathologist, Caterina Giannini MD, PhD, and neuro-radiologist, Patrick H. Luetmer, MD, of the Mayo Clinic provided insightful commentary to the challenging and interesting cases. The best Walsh paper was “A Bitter-Sweet Diagnosis” by Rebecca Stacy, MD, from Massachusetts Eye and Ear Infirmary.

The symposia this year included understanding the melanopsin pathway and its contributions to the pupillary function, sleep, and photophobia. “Controversies in Neuro-ophthalmology” highlighted different opinions in the work-up of anisocoria, whether multiple sclerosis and neuromyelitis optica are the same disorder, and treatment options for hereditary optic neuropathies. The “Neuro-ophthalmology of Cancer” highlighted the current treatment of neoplasms that involve the visual pathways as well as paraneoplastic immunology and syndromes. “OCT in Neuro-ophthalmology Practice” and “Thyroid Eye Disease” rounded out the symposia.

The 2010 Dan Jacobson lecturer, Deborah Friedman, MD, MPH, reviewed a variety of diagnostic and therapeutic issues regarding idiopathic intracranial hypertension in “IIH with Dan and Beyond.”

Platforms and Poster sessions highlighted outstanding research being done by medical students, residents, fellows, and members of NANOS. The best presentation by a medical student was Jonathan Frandsen (M2) from the University of Utah, for his paper: Macular cartenoids in patients with photophobia.

Best presentation by a resident was Patrick Yu-Wai-Man, MD, from the Mitochondrial Research Group, Newcastle University, United Kingdom. His presentation was “Multi-system neurological disease is common in patients with OPA1 mutations.”

The best presentation by a fellow was Robert Avery, DO, from The Children’s Hospital of Philadelphia. His presentation was entitled: “Reference range of cerebrospinal fluid opening pressure in children.”

NANOS honored Jonathan Trobe, MD, at the banquet for his excellent service as the third editor of the Journal of Neuro-ophthalmology—2001–2009.

NANOS awarded Larry Frohman, MD, the Distinguished Service Award, the organization’s highest honor. Dr. Frohman has been on the board for 14 years. He has served many positions including president-elect, president, and chair of the board. He is currently the NANOS treasurer. In giving the award, Dr. Deborah Friedman noted that besides all of the positions he has held for NANOS, Dr. Frohman created the Walsh Compendium in 1994, started the NANOS slide exchange, championed practice issues in neuro-ophthalmology, and secured grant funding for the Neuro-ophthalmology Virtual Education Library.

Janel Fick, the administrative director from L & L Management Services, Minneapolis, Minnesota, made certain of a well-run meeting and fun-filled social events.