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Instructions for Contributors will appear in this journal annually in the March issue.
Acute Effects of Sildenafil (Viagra) on Blue-on-Yellow and White-on-White Humphrey Perimetry

Timothy J. McCulley, MD, Byron L. Lam, MD, Michael F. Marmor, MD, Kara B. Hoffman, MD, James K. Luu, MD, and William J. Feuer, MS

Objective: To study the effects of sildenafil on blue-on-yellow and white-on-white Humphrey visual field (HVF).

Materials and Methods: Healthy subjects, ages 20 to 38 years, were prospectively randomized to active drug (n = 5) or placebo (n = 3) groups. Blue-on-yellow and white-on-white HVF testing was performed before and 1 hour after masked dosing of sildenafil 200 mg or placebo. Changes in mean deviation (MD) were compared between groups.

Results: Three of three placebo and four of five sildenafil subjects had no change on HVF. One of five sildenafil subjects had a decrease in MD of 17.9 dB and 4.7 dB on blue-on-yellow and white-on-white HVF testing, respectively. This subject reported more systemic side effects than other subjects.

Conclusions: Sildenafil has no effect on HVF testing in most persons; however, sildenafil caused an acute abnormality of HVF testing in one subject, who experienced pronounced non-visual systemic symptoms; this effect was greater on blue-on-yellow than white-on-white HVF.

Key Words: Humphrey visual field—Ophthalmology—Side effects—Sildenafil—Viagra.

Sildenafil (Viagra, Pfizer, New York, NY), a selective phosphodiesterase 5 (PDE5) inhibitor, has a 10% cross activity on PDE6, which is involved in phototransduction in retinal photoreceptors (1–3). Some individuals report bluish vision, increased light sensitivity, or diminished color perception, lasting up to hours after ingestion of sildenafil (4). A lack of acute changes in white-on-white Humphrey visual field (HVF) testing has been reported (5), and no long-term visual symptoms or dysfunction have been found. This study evaluates effects of sildenafil on blue-on-yellow and white-on-white HVF testing.

METHODS

After obtaining institution-reviewed informed consent, eight healthy subjects were prospectively randomized, based on the order in which they volunteered, and received active drug (n = 5, 4 women and 1 man, ages 20–38 years) or placebo (n = 3, 3 women, ages 21–28 years). Subjects were blind to which pill they received. The large percentage of women occurred because more women volunteered. Both eyes of each subject were tested with white-on-white (fastpac 30-2, size 3 stimulus) followed by blue-on-yellow (fastpac 30-2, size 5 stimulus) HVF analyzer, before and 1 hour after ingesting sildenafil 200 mg or placebo. Changes in mean deviation (MD) were then compared between groups. For analysis, the MD of both eyes was averaged. No significant difference between the HVF of the OD and OS was found in any subject.

### TABLE 1. Effect of sildenafil on Humphrey visual fields

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Group</th>
<th>Visual symptoms</th>
<th>HVF MD (dB) white-on-white baseline</th>
<th>HVG MD (dB) white-on-white repeat</th>
<th>HVF MD (dB) blue-on-yellow baseline</th>
<th>HVF MD (dB) blue-on-yellow repeat</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>F</td>
<td>Sildenafil</td>
<td>Yes</td>
<td>-1.63</td>
<td>-6.29</td>
<td>0.73</td>
<td>-17.10</td>
</tr>
<tr>
<td>2</td>
<td>38</td>
<td>M</td>
<td>Sildenafil</td>
<td>Yes</td>
<td>-2.26</td>
<td>-1.77</td>
<td>-2.14</td>
<td>0.16</td>
</tr>
<tr>
<td>3</td>
<td>32</td>
<td>F</td>
<td>Sildenafil</td>
<td>No</td>
<td>-5.15</td>
<td>-5.07</td>
<td>-11.92</td>
<td>-11.64</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>F</td>
<td>Sildenafil</td>
<td>No</td>
<td>-3.11</td>
<td>-2.25</td>
<td>-2.02</td>
<td>-2.50</td>
</tr>
<tr>
<td>5</td>
<td>28</td>
<td>F</td>
<td>Sildenafil</td>
<td>No</td>
<td>-4.31</td>
<td>-2.66</td>
<td>-7.25</td>
<td>-4.38</td>
</tr>
<tr>
<td>6</td>
<td>28</td>
<td>F</td>
<td>Placebo</td>
<td>No</td>
<td>-3.93</td>
<td>-4.55</td>
<td>-6.71</td>
<td>-10.74</td>
</tr>
<tr>
<td>7</td>
<td>22</td>
<td>F</td>
<td>Placebo</td>
<td>No</td>
<td>-1.67</td>
<td>-0.17</td>
<td>-2.78</td>
<td>-3.17</td>
</tr>
<tr>
<td>8</td>
<td>28</td>
<td>F</td>
<td>Placebo</td>
<td>No</td>
<td>-2.16</td>
<td>-1.92</td>
<td>-5.08</td>
<td>-4.58</td>
</tr>
</tbody>
</table>

HVF, Humphrey visual field; MD, mean deviation.
RESULTS

Table 1 summarizes the results. One sildenafil subject, a 20-year-old woman, developed bilateral superior field depression with a 17.8-dB decrease in MD on blue-on-yellow and bilateral infranasal depression with a 4.7-dB decrease in MD on white-on-white HVF (Fig. 1). In addition to severe flushing and headache, which was experienced to a lesser degree by all sildenafil subjects, this subject reported abdominal discomfort. She was also one of two subjects who reported visual symptoms of a bluish haze and flashing lights. The remaining four sildenafil subjects performed similarly to the placebo group on blue-on-yellow (mean change in MD ± standard deviation, 1.24 ± 1.60 dB and -1.31 ± 2.40 dB, respectively, \( P = 0.15 \), \( t \) test) and white-on-white (mean MD change, 0.8 ± 0.66 dB and 0.37 ± 1.07 dB, respectively, \( P = 0.54 \), \( t \) test) HVF perimetry.

DISCUSSION

After ingesting 200 mg sildenafil, most subjects had no detectable changes on blue-on-yellow or white-on-white HVF, including one sildenafil subject, who was tested while experiencing visual symptoms. This is consistent with previous published results (5). One of five sildenafil subjects performed poorly on HVF testing, with blue-on-yellow affected more than white-on-white. Severe nonvisual systemic side effects may have interfered with her test performance and may have been responsible for some of the observed changes; however, the reliability indices were good, which is not consistent with functional changes or an inability to concentrate. The relevance of this idiosyncratic response to sildenafil intake remains to be determined until more subjects have been tested.

REFERENCES

Visual Loss and Recovery in a Patient With Friedreich Ataxia

Syndee J. Givre, MD, PhD, Michael Wall, MD, and Randy H. Kardon, MD, PhD

A 15-year-old boy with genetically confirmed Friedreich ataxia (FRDA) sought treatment at the Pediatric Ophthalmology Clinic at the University of Iowa Hospitals and Clinics for 2 to 3 months of gradually progressive, painless visual loss OS. He was otherwise in his usual state of health.

According to the parents, the patient began experiencing clumsiness at the age of 9 years. Within 4 years, he was confined to a wheelchair because of problems with balance. FRDA was diagnosed at the age of 15 years, when genetic analysis indicated approximately 1,000 repeats of the GAA repeat region of each allele of the frataxin (FRDA) gene. Associated conditions included mild left ventricular hypertrophy and scoliosis. He also had a history of peptic ulcer disease with positive serology for Helicobacter pylori. His only medication was cisapride (Propulsid, Janssen Pharmaceuticals, Titusville, NJ).

Ten months before presentation, the best-corrected acuity documented at a local optometrist’s office was 20/30 OD and 20/30 OS. On presentation, best-corrected visual acuity was 20/30-1 OD and 20/70-2 OS. Color vision was significantly decreased OU when using Ishihara plates (3/14 plates OD; 2/14 plates OS). Critical foveal flicker fusion, a measure of optic nerve conduction, was moderately depressed at 20.6 Hz ± 3.3 Hz OD and 17.0 Hz ± 5.7 Hz OS (normal = 30 Hz). Extraocular motility was full OU, and the patient was orthophoric in all fields of gaze. Kinetic perimetry (Goldmann bowl perimeter) results from the first visit are shown in the top row of Figure 1. There was generalized depression, OS worse than OD. The slit-lamp and fundus examinations were normal OU, including optic disc appearance. A multifocal electroretinogram (MERG) was obtained to help differentiate between retinal and optic nerve dysfunction. This test records the topographic electrical response from the photoreceptors and bipolar cells of the retina (1). It indicated normal retinal function within the central 50° (diameter) of field. DNA analysis for known mutations associated with Leber hereditary optic neuropathy was negative. Magnetic resonance imaging (MRI) of the brain and orbits without and with contrast was normal; there was no enhancement of the optic nerves. Despite this, a trial of corticosteroids, intravenous followed by oral, was instituted. There was no improvement, and over the next few months, the visual acuity and visual fields continued to worsen. The worst recorded acuities were 20/200 OD and 20/100-2 OS, 5 months after the onset of visual symptoms. At this time, the patient was unable to detect the critical foveal flicker fusion stimulus with either eye. Goldmann perimetry results had also worsened (see second row of Fig. 1). The pattern of visual field loss on Goldmann perimeter recordings obtained several months apart was repeatable except for deepening of existing relative scotomata. This provides evidence that the vision loss was physiologic.

Approximately 10 months after his symptoms began, the patient and his family members independently noted an improvement in his visual functioning. He became able, for example, to read a clock located at a fixed distance from his bed, which he previously had been unable to see. On examination, his visual acuity was 20/125 OD and 20/80+3 OS. Three months later, the acuity had improved to 20/50-2 OD and 20/40-3 OS. Goldmann perimetry from this day showed recovery of the III4e and I4e isopters centrally OD and was essentially unchanged OS (see the bottom row of visual fields in Fig. 1). Both optic discs showed mild temporal pallor.
Regarding possible factors related to recovery, no recent change in diet or medication was noted. The only change in lifestyle had been a reduction in the patient's level of physical activity because of immobilization after a T2-sacral spine fusion for scoliosis. The surgery had been performed 3 months before the onset of visual improvement.

**DISCUSSION**

In the past, patient diagnosis and the classification of hereditary ataxias was made difficult by the presence of overlapping clinical features among the various entities and by incomplete understanding of the underlying genetics. Early case series of FRDA were likely contaminated with misdiagnosed patients. Despite this, and even before the identification of the genetic defect, distinguishing features of this disorder had been agreed on (2-5). FRDA is an autosomal recessive disorder that usually presents at the time of puberty and almost always before the age of 25 years. Typically, there is progressive truncal and limb (upper and lower) ataxia and loss of tendon reflexes in the legs. Axonal, sensory neuropathy, reduction in joint position or vibration sense in the legs, dysarthria, and extensor plantar responses often occur as well. Associated problems include scoliosis, pes cavus, cardiomyopathy, and diabetes mellitus. Not all patients have all of these findings, and the exact signs required for the diagnosis of FRDA are still a matter of debate. Before the availability of genetic testing, most authors relied on data from the clinical series of Geoffroy et al. (3) and Harding (4). Neuropathologic investigation has indicated involvement of the cerebellum, spinal cord, and peripheral nerves (6,7). Neuroradiologic abnormalities may be absent or include atrophy of the brainstem (mostly medullary) and cerebellum (8).
Neuro-ophthalmologic manifestations of FRDA include oculomotor abnormalities such as nystagmus, ocular flutter, and impairment of the vestibulo-ocular reflex (9–11) as well as vision loss with optic atrophy (3,4,12,13). The degree and mechanism of vision loss has not been well characterized; nor has it been investigated in a detailed, controlled manner. When it has been addressed, authors, usually nonophthalmologists, have reported on visual acuity and optic atrophy as assessed by ophtalmoscopy or visual evoked potentials (VEP). Table 1 summarizes the available data on visual loss in FRDA since 1976. By this time, a reasonable consensus on the clinical characteristics of the disorder had been reached, so the papers cited likely only include FRDA patients. The most extensive clinical review of vision loss is probably that of Carroll et al. (12), who measured at least visual acuity in 22 patients. None had acuity worse than 20/80. Fourteen of the 22 had prolongation of the P100 latency on VEPs. Fifteen patients had fundus examinations, and mild to moderate optic disc pallor was observed in nine of them. Three patients underwent full-field electroretinography; all showed 'just subnormal' responses not thought to be significantly contributing to the abnormal VEPs. Based on these data and similar, though less systematically investigated, findings by other authors, the mechanism of vision loss in FRDA is presumed to be an optic neuropathy (Harding [4] did report one patient with a peripheral retinal pigmentary disturbance). Abnormalities of the optic tract and lateral geniculate nucleus have been observed at postmortem histologic examination (6).

The affected gene in FRDA has been mapped to chromosome 9q13-q21.1 (14–16) and the encoded protein, frataxin, identified (17,18). Ninety-four percent to 98% of FRDA patients are homozygous for an expansion of the GAA repeat region of the gene (13,18). Normally, there are 7 to 22 GAA repeats in this region of the FRDA gene. Patients with FRDA have, on average, 600 to 800

<table>
<thead>
<tr>
<th>Study</th>
<th>Visual acuity</th>
<th>Optic atrophy</th>
<th>VEP abnormality</th>
<th>Color vision</th>
<th>Visual field</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andermann et al., 1976</td>
<td>3/58 (5%) Patients with “markedly decreased visual acuity”</td>
<td>4/58 (7%) Patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geoffroy et al., 1976</td>
<td>22/50 (44%) Patients with decreased visual acuity which we found to be almost always due to partial optic atrophy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carroll et al., 1981</td>
<td>(a) 27/43 (63%) Eyes “normal”</td>
<td>10/18 Eyes from (a)</td>
<td>52% of eyes from (a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(b) 7/43 (16%) Eyes worse than 20/20 but equal to or better than 20/50</td>
<td>5/5 Eyes from (b)</td>
<td>86% of eyes from (b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(c) 5/43 (21%) Eyes worse than 20/50</td>
<td>5/5 Eyes from (c)</td>
<td>100% eyes from (c)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harding et al., 1981</td>
<td>14/115 (12%) Patients had “normal” vision but optic atrophy</td>
<td>Total 35/115 (30%) patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>13/115 (11%) Patients had “mildly decreased vision” and optic atrophy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11/115 (5%) Patients had “severely decreased vision” and optic atrophy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Livingston et al., 1981</td>
<td>(d) 15/42 (36%) Eyes 20/20 or better</td>
<td>33% Eyes from (d)</td>
<td>33% eyes from (d)</td>
<td>Normal in 19/19 patients (2 patients with 20/20 vision not tested)</td>
<td>Normal in 19/19 patients (2 patients with 20/20 vision not tested)</td>
</tr>
<tr>
<td></td>
<td>(e) 19/42 (45%) Eyes worse than 20/20 but equal to or better than 20/50</td>
<td>53% Eyes from (e)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Durr et al., 1996</td>
<td>“reduced” in 13% of 40 genetically confirmed patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monterini et al., 1997</td>
<td></td>
<td>21% of 109 Patients with genetically confirmed FRDA</td>
<td></td>
<td></td>
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</tbody>
</table>

FRDA, Friedrich ataxia; VEP, visual evoked potential.
confinement to a wheelchair and directly proportional to inversely proportional to the age of onset and time until GAA repeats (13,18,19). The number of GAA repeats is expressed in human heart, liver, skeletal muscle, pancreas, and central nervous system. This, for the most part, corresponds to the sites of pathology in FRDA. In developing mice, in situ hybridization indicated expression of frataxin transcripts in brown adipose tissue (which contains many mitochondria; see later discussion), brains, spinal cord, liver, heart, and kidney (21).

Both a yeast homologue of frataxin, YHFI, and a mouse homologue have been studied (21–23) in these organisms, as well as in human tissue culture lines, the protein localizes to mitochondria. Deletion of the YHFI gene in yeast leads to decreased production of mitochondrial DNA and hypersensitivity to oxidative stress. Specifically, Babcock et al. (22) found that YHFI gene deletion results in iron accumulation in mitochondria. It has been postulated that expression of abnormal frataxin in mitochondria could lead to an overload of iron, which, in turn could result in damage to mitochondrial DNA, production of toxic hydroxyl radicals or, simply, interference with the respiratory chain (22,24). Recently, in vivo phosphorescent magnetic resonance spectroscopy showed decreased adenosine triphosphate (ATP) production in calf muscles of FRDA patients as compared with normal controls (25). This same study showed a negative correlation between the rate of mitochondrial ATP production and the number of GAA repeats in the FRDA genes of patients. Based on abnormal biochemical studies in patients with FRDA, this disorder was thought to involve mitochondrial energy deprivation long before the gene and its product had been determined (26).

Although FRDA is linked to the nuclear genome, it may share a final-common-pathway mechanism with optic neuropathy linked to mitochondrial inheritance, such as Leber hereditary optic neuropathy (LHON) or with acquired optic neuropathies such as the Cuban epidemic optic neuropathy. The exact ways in which mitochondrial dysfunction leads to optic nerve damage are unknown. In LHON, it has been postulated to involve mitochondrial energy deprivation long before the gene and its product had been determined (26).

Two features of the case described in this report are unusual. First, our patient’s visual acuity loss was profound as compared with that of most patients reported in the literature. This may be related to the large number of GAA repeats on both alleles that his genetic analysis revealed. His early age of onset and the early age at which he required a wheelchair support this. Whether the variability in optic atrophy seen in FRDA is related to the duration of disease or the number of GAA repeats is still in question (13,20). Second, there was partial recovery of visual acuity and visual fields. This has not been previously documented in the literature. The mechanism is unknown but may be similar to the mechanism of spontaneous recovery of vision, which has been noted in LHON (29–33).

REFERENCES

Short Communications

Central Retinal Artery Occlusion After a Local Anesthetic With Adrenaline on Nasal Mucosa

Tarja H. Maaranen, MD, and Maija I. Mäntyjärvi, MD

The purpose of this article is to describe a 75-year-old patient with an acute central retinal artery occlusion after a local anesthetic with adrenaline on nasal mucosa. The local anesthetic was used in removing Jackson tubes from the left lacrimal canal. Occlusion of the central retinal artery related to nasal operations is a rare complication. In previous reports, retinal artery occlusions have been noted in connection with nasal submucosal injections of anesthetic and epinephrine. In our case, the use of anesthetic and adrenaline was superficial.

Key Words: Adrenaline—Central retinal artery occlusion—Lidocaine—Local anesthetic.

Loss of vision because of central retinal artery occlusion after an operation in the eye region is a rare but serious complication. Occlusion of central retinal artery has been reported after a nasal submucosal injection of local anesthetic with epinephrine (1) and in connection with nasal steroid injections (2). Also, superficial use of cocaine (3) and oxymethazoline hydrochloride (4) on the nasal mucosa has been reported to cause retinal artery occlusion.

We describe a case in which intranasal lidocaine with adrenaline caused an acute central retinal artery occlusion and permanent loss of vision in our patient. The lidocaine and adrenaline were used superficially on the nasal mucosa.

CASE REPORT

A 75-year-old man had had disturbing lacrimation on the left side for a long time. In June 1998, a Jackson silicone tube was installed in the left lacrimal system under general anesthesia in the Eye Clinic of the University Hospital of Kuopio. At the time of this procedure, his visual acuity was normal OU, he did not complain of any visual disturbances, and there was no history of visual impairment in either eye.

The Jackson tube was left in situ for 6 months. In November 1998, the patient revisited our clinic for the removal of the silicone tube. The patient still had normal visual acuity OU. The tube was cut, but it did not come out when the patient blew his nose, and the tube was not visible in the nose. The patient was sent to an otorhinolaryngologist, who put a cotton stick moistened with lidocaine hydrochloride (40 mg/ml) and adrenaline hydrochloride (1 mg/ml) into the left nostril for a few minutes. Thereafter, the tube was removed.

About 20 minutes later, the patient noticed impairment of the visual acuity OS. The patient immediately came back to our clinic, and a typical acute central retinal artery occlusion was diagnosed OS. The patient could see only hand motions OS. The arterioles were strongly attenuated, and the retina was pale OS. The eye was treated with an anterior chamber paracentesis, 0.5 mg of nitroglycerine was given orally, and 500 mg of acetazolamide was administered intravenously. However, visual acuity OS did not improve.

The patient had a history of two cardiac infarcts, in 1973 and 1986. In 1992, he had a coronary bypass operation. Before this loss of visual acuity, the patient had no arrhythmia, chest pain, or transient ischemic attack (TIA). An internist examined the patient, and no ischemic or other changes in the heart could be noticed; the patient did not have systemic arterial hypertension, and there was no significant narrowing in the cervical arteries in the ultrasonic examination. The blood count was normal.

DISCUSSION

A local anesthetic, lidocaine with adrenaline, was superficially used on the nasal mucosa in the removal of a Jackson tube. In two previous reports, superficial use of
vasoconstrictive agents has been reported to cause retinal artery occlusion. Wallace et al. (3) reported a case of central retinal artery occlusion 4 hours after intranasal administration of cocaine. In this case, vasospasm has been suggested as mechanism of retinal artery occlusion. Magargal et al. (4) reported a case in which chronic use of oxymetazoline hydrochloride caused a branch retinal artery occlusion. In our case, adrenaline probably caused vasoconstriction in the central retinal artery through the ethmoidal arteries.

To our best knowledge, there are no previous reports of central retinal artery occlusions caused by superficial use of anesthetic and adrenaline. Savino et al. (1) reported four cases in which intranasal injection of a local anesthetic and epinephrine caused retinal artery occlusion. All of these patients had had nasal surgery under general anesthesia. Retinal artery occlusion was diagnosed several hours or days after the anesthesia. The mechanism of artery occlusion in these cases could have been surgical trauma, vasospasm, or embolism. In the current case, the mechanism is probably vasospasm, because the visual loss developed quickly after using lidocaine and adrenaline, and the retinal arterioles were strongly attenuated.

Applying superficial anesthetic and adrenaline to the nasal mucosa can cause vasoconstriction in the retinal arteries. Older patients, such as in our case, can have some degree of arteriosclerosis narrowing the lumens of blood vessels. Even a small amount of vasoconstrictive agent can cause an occlusion in this situation. Thus, adrenaline should be avoided if possible or used with caution in nasal operations on older patients.

REFERENCES

The Neuro-ophthalmologic Complications of Cervical Manipulation

Michael W. Devereaux, MD

Cervical manipulation, specifically chiropractic manipulation, is an important cause of vertebrobasilar and occasionally carotid distribution strokes. Neuro-ophthalmologic findings are a common and at times relatively isolated feature of cervical manipulation-induced stroke. A case of chiropractic-induced occipital lobe infarction with homonymous hemianopsia is reported, and the literature regarding neuro-ophthalmologic findings is reviewed.

Key Words Cervical manipulation—Chiropractic—Extracranial arterial dissection—Hemianopsia—Stroke.

Neurologic complications secondary to neck manipulation, specifically chiropractic manipulation, are known to neurologists but not well known to the public. The major categories of injury include stroke, myelopathy, and cervical radiculopathy. The frequency, although debated, may be greater even than that stated in the literature (1-16). Neuro-ophthalmologic complications are almost always the result of ischemia/infarction secondary to injury to one or both vertebral arteries and far less frequently to a carotid artery (17,18). Most often, the neuro-ophthalmologic findings appear as part of a constellation of findings indicative of a major stroke, usually in the brain stem, most often in the lateral medullary tegmentum (Wallenberg syndrome) (3-16).

Occasionally, however, relatively isolated neuro-ophthalmologic symptoms and signs may occur after chiropractic cervical manipulation. The cause may be missed unless the patient is carefully questioned. This is particularly true because there may be a long time between the manipulation and the cerebrovascular event (16,19,20).

We have documented four patients with post-chiropractic vertebrobasilar distribution events at University Hospitals of Cleveland (UHC) who were cared for by two members of the Department of Neurology in the last 5 years. One patient had an isolated neuro-ophthalmologic presentation.

CASE

A 34-year-old healthy woman with a 2-week history of neck pain had three chiropractic treatments during this period. On the drive home from the third treatment, she noted that she could not see well to the right. She saw her ophthalmologist the next day, and he identified a right visual field disturbance. She was admitted to UHC later that same day.

There was no history of visual disturbance, migraine headache, or smoking. She was not taking birth-control pills. The only past medical problem was asthma.

Results of the neurologic examination were normal, with the exception of a dense right congruous homonymous hemianopsia.

Diagnostic tests:
- Magnetic resonance imaging (MRI): Left occipital lobe ischemic infarct
- Magnetic resonance angiography (MRA): Right vertebral artery dissection at the C1 level and occlusion of the calcarine branch of the left posterior cerebral artery.

She was anticoagulated with heparin and sent home 4 days later on warfarin.

A follow-up visit, 4½ months after discharge, indicated a persistent right homonymous hemianopsia.

Diagnostic tests:
- MRI: 2-cm area of encephalomalacia, left occipital lobe
- MRA: Normal, with exception of slight irregularity of right vertebral artery lumen

Anticoagulation was stopped and aspirin started. Approximately 16 months after the stroke, I spoke to her by telephone, and she still had a right visual field disturbance (her lawyer would not permit a follow-up visit).

DISCUSSION

The vertebral arteries pass through the transverse foramina of the first six vertebrae of the highly mobile cervical spine, which permits approximately 160° of rotation, most of which occurs between the skull and the...
C3 vertebra. Approximately 90° of this rotation occurs between the axis and the atlas at the level of the atlas loop of the vertebral artery. Neck manipulation, particularly a combination of rotation and tilting, stretches the vertebral artery, producing a shearing force on this segment at the level of the atlantoaxial joint. This may result in an intimal tear with resultant occlusion of the lumen, thrombus formation, and embolization (9,17,21,22). A pseudo-aneurysm also may form in the vessel wall, producing occlusion (Fig. 1) (5,8,23).

Brown and Tatlow (23) angiographically showed occlusion of the vertebral artery in 5 of 41 cadavers subjected to simultaneous full head extension and 90° of rotation to the side opposite the occlusion. This indicates how potentially susceptible the vertebral arteries may be to head/neck manipulation. Repeated neck manipulation also may produce subclinical changes in the vertebral arteries (16,19,20). The accumulation effect then may result in a subsequent stroke at a later date (16,19,20). Carotid artery dissection also may occur with neck rotation secondary to compression of the internal carotid artery against an upper cervical vertebra (9,17,18).

Vertebrobasilar, and less commonly, carotid artery distribution vascular events can be the result of nontherapeutic mechanical injury to the neck (Table 1) as well as therapeutic neck manipulation (Table 2). Therapeutic neck and back manipulation is an ancient art (29,30). The best known modern iterations, chiropractic and osteopathy, are both late nineteenth century American, midwestern inventions (31). Osteopathic manipulation in theory relieves symptoms by improving circulation to the spine, whereas chiropractic manipulation works by reducing subluxations that cause nerve-root compression. In 1895, Daniel David Palmer, a dry goods grocer and later a magneto-therapist on a quest to discover a unified concept to explain human illness, by chance manipulated a "vertebra racked from its normal position," on Harvey Lillard, a janitor claiming deafness for 17 years (30). The deafness was relieved. Palmer subsequently theorized that all disease is the result of interference with the body's "innate intelligence" by misaligned vertebrae (30). He coined the term chiropractic from the Greek cheiro (hand) praktikas (practice) and founded the Palmer School of Chiropractic in Davenport, Iowa. The chiropractor uses different manipulations and mobilization techniques. The most common are a low-velocity, high-amplitude method consisting of a series of gentle and repeated motions delivered to a point, and a high-velocity, low-amplitude method consisting of a sudden thrust delivered to the involved vertebrae (1,29). No studies have indicated which method is more likely to cause arterial injury (1,32).

Neuro-ophthalmologic symptoms and signs may be the most prominent and sometimes the primary manifestation of a cerebrovascular insult after chiropractic manipulation (Table 3). The most common are visual-field disturbances secondary to occipital lobe strokes, as is the case with my patient, (6,8,11,33-35) Frisoni and Anzola (11) reported that 5% of the 72 cases they reviewed had occipital strokes. Quadrantanopias, hemianopias, and bilateral visual field disturbances also occur. Horner syndrome, in the absence of Wallenberg syndrome, also may occur (8,33,36). Grayson (36) theorized that in one case cervical manipulation produced direct injury to a white ramus communicans with a resultant Horner syndrome.

Two cases of internuclear ophthalmoplegia (INO) after cervical manipulation have been reported (37,38); both had other neurologic findings. In addition, Sherman
et al. (8) reported a case of INO as a result of head turning while backing up a car. Other complications of manipulations include sixth nerve palsy (8), gaze palsy (8,27), painful ophthalmoplegia (39), central retinal artery occlusion (40), and relatively isolated nystagmus (11,12).

Does the therapeutic benefit of cervical manipulation justify the complication rate? The first problem in answering this questions is that the rate of complication is not fully established (15,32,41-43). Only approximately 200 cases of cerebrovascular events have been reported, but a survey conducted on a small number of California neurologists adds 56 strokes to this number (1). I strongly suspect, based on the literature and personal experience, that a large number of cases are recognized but not reported. Probably additional cases of stroke exist in which the temporal relationship with chiropractic manipulation has gone unrecognized.

With regard to low back chiropractic manipulation, a few studies have attempted to show benefit. The meta-analysis by Shekelle et al. (44) is often cited, but the benefit was minimal at best, and the results have been challenged (43). Other studies have shown essentially no benefit (45,46).

Regarding benefit from cervical manipulation for neck pain and headache, a meta-analysis by Hurwitz et al. (42) concluded by stating, “cervical spine manipulation and mobilization probably provides at least some short-term benefits for some patients with neck pain and headache”, hardly a ringing endorsement. Barr (47), commenting on this study, stated that there are “no convincing data to support manual therapy.”

CONCLUSION

Stroke is a well-described consequence of chiropractic manipulation. Neuro-ophthalmologic disorders may be the primary and occasionally the sole manifestation of chiropractic-induced cerebrovascular injury. The frequency of chiropractic-induced stroke is uncertain but probably more common than currently appreciated. Patients presenting with stroke, particularly if relatively young; without stroke risk factors; and with evidence of vertebral artery dissection by MRA, should be questioned about recent chiropractic manipulation. Patients should be made aware of the lack of established benefit of chiropractic cervical manual therapy and the potential risk of neurologic injury.

Acknowledgement: Robert B. Daroff, MD, reviewed this manuscript and provided helpful comments.

REFERENCES

Superior Oblique Palsy in a Patient With a History of Perineural Spread From a Periorbital Squamous Cell Carcinoma

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A 74-year-old man experienced vertical diplopia. Two years earlier, he was diagnosed with a squamous cell carcinoma of the periorbital frontal skin, with perineural spread involving the opthalmic division of the right trigeminal nerve and the right facial nerve. The clinical findings were consistent with a right fourth cranial nerve palsy. Computerized tomography and magnetic resonance imaging demonstrated a discrete mass involving the belly of the right superior oblique muscle. An anterior orbitotomy and biopsy demonstrated a mass extending into the belly of the superior oblique muscle. Histology revealed an infiltrating squamous cell carcinoma. The possibility of perineural, direct, or metastatic spread to the superior oblique muscle should be considered in a patient with a history of squamous cell carcinoma of the head and neck. The authors believe this case to be the first report of superior oblique underaction due to involvement of the muscle by squamous cell carcinoma, presumably because of perineural spread. Diagnosis was made possible by neuroimaging and histopathology. There was good short-term resolution of the patient's diplopia after radiotherapy.

Key Words: Diagnosis—Perineural spread—Squamous cell carcinoma—Trochlear nerve.

Superior oblique palsy is the most common cause of vertical ocular motor palsies in adults (1). Metastatic disease is a recognized but rare cause of superior oblique palsy. In humans, carcinomas most commonly arise from skin (2), and Australia has the highest incidence of skin cancer in the world (3).

Perineural spread (PNS) is a well-recognized complication in patients with squamous cell carcinomas (SCCs) (4). Perineural spread is also a significant prognostic indicator because the cranial nerves provide a direct route of spread to the brainstem. Tumors that are capable of PNS have a higher incidence of blood-born metastases to distant sites (5). A high level of suspicion for PNS may improve the chance of cure with early radical surgery and radiotherapy. However, once the bony foramina have been traversed by the tumor, treatment is largely palliative.

CASE REPORT

A 74-year-old man had a 1-week history of vertical diplopia. His medical history included multiple excisions of skin cancers from his head and neck. Two years earlier, he was diagnosed with PNS from a forehead SCC involving the opthalmic division of the right trigeminal nerve and the temporal and zygomatic branches of the right facial nerves. On examination, using the Parkes three-step test, a right fourth nerve palsy was diagnosed. There was reduced sensation to pin-prick and light touch in the distribution of the ophthalmic division of the right trigeminal nerve. The muscles supplied by the zygomatic and temporal branches of the right facial nerve were weak. Results of the remainder of the cranial nerve examination were normal.

Because of the patient's history of PNS, computerized tomography of the head was performed, and it demonstrated a 1.5-cm discrete mass in the right superomedial orbit, which was indistinguishable from the belly of the superior oblique muscle (Figs. 1, 2). There was no enlargement of bony foramina. Magnetic resonance imaging revealed no centripetal spread of the tumor along the trochlear nerve, into the brainstem, or intracranially. In particular, the cavernous sinus was normal. To obtain a tissue diagnosis, a superomedial anterior orbitotomy was performed and a biopsy was taken. Histopathology demonstrated cords of infiltrating SCC (Fig. 3).

The patient subsequently underwent a course of radiotherapy to the region, and there was resolution of his diplopia. Unfortunately, there was recurrence of his orbital disease and involvement of his cervical lymph nodes. The patient died 3 years later, after a brainstem vascular event. An autopsy was denied.
SUPERIOR OBLIQUE PALSY

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FIG. 1. Coronal computed tomography scan of the orbits demonstrates an enlarged right superior oblique muscle (arrow).

DISCUSSION

A fourth nerve palsy is the most common cause of vertical ocular motor palsies in adults. It should therefore be suspected in any patient with a vertical deviation and/or abnormal head posture. However, it is the least prevalent cause of an isolated ocular motor paralysis (6). In a study by Rush and Young (7), of 1,000 cases of paralysis of cranial nerves III, IV, and VI, the most common cause of a fourth nerve palsy remained undetermined (36%). Other causes included trauma (32%), vascular disease (18%), neoplasm (4%), aneurysm (2%), and miscellaneous causes (8%). Uncommon reported cases included an arteriovenous malformation of the trochlear nerve (6), intracavernous internal carotid aneurysm (7), a large basilar aneurysm (7), a tentorium cerebelli meningioma (8), and a posterior fossa astrocytoma (9). Orbital myositis can also involve the superior oblique muscle (10). Metastasis to extracocular muscles, in particular to the medial rectus, can occur (11), as in a case of small cell cancer that metastasized to the medial rectus muscle. However, metastatic disease to the orbit is usually diffusely spread within the orbit, rather than confined to a discrete mass within one extracocular muscle (12).

Periorbital skin cancers (1,2) are the most likely cause of PNS affecting the cutaneous branches of the trigeminal and facial nerves. Although our patient had a history of PNS of an upper facial SCC to the facial and trigeminal nerves, the mechanism of the tumor reaching the superior oblique muscle is uncertain. The possibilities include direct, metastatic, or PNS of the SCC.

REFERENCES

Sixth Nerve Palsy as a Presenting Sign of Intracranial Plasmacytoma and Multiple Myeloma

Tammy Z. Movsas, MD, Laura J. Balcer, MD, MSCE, Eric R. Eggenberger, DO, Jay L. Hess, MD, PhD, and Steven L. Galetta, MD

Multiple myeloma and plasmacytoma are rare causes of mass lesions at the skull base and cavernous sinus. Sixth nerve palsy, in isolation or in combination with other cranial neuropathies, may occur rarely as the initial presenting feature of multiple myeloma. We report the neuro-ophthalmologic, radiologic, and pathologic findings for two patients who developed sixth nerve palsies as an initial manifestation of intracranial plasmacytoma and multiple myeloma. One patient presented with an isolated sixth nerve palsy in the setting of multiple vasculopathic risk factors. Treatable skull base lesions, including plasmacytoma and multiple myeloma, must be considered in patients with sixth nerve palsies, especially among those who demonstrate a progressive course or multiple cranial neuropathies.

Key Words: Diplopia—Hypoglossal nerve—Multiple myeloma—MR imaging—Plasmacytoma—Sixth nerve.

Sixth nerve palsy, in isolation or combination with other cranial neuropathies, has rarely been described as the initial presenting feature of intracranial plasmacytoma or multiple myeloma (1,2). In fact, less than 4% of all cases of cavernous sinus syndrome have occurred in the setting of multiple myeloma (3). We describe two patients who developed binocular horizontal diplopia as the initial manifestation of intracranial multiple myeloma and plasmacytoma. Patient characteristics are summarized in Table 1.

CASE REPORTS

Case 1
A 78-year-old woman with a history of diabetes mellitus, hypertension, coronary artery disease, hypercholesterolemia, and atrial fibrillation presented with binocular horizontal diplopia that was worse in right gaze. The diplopia had progressed over 1 month. A right frontal headache was noted 1 week after the onset of diplopia. There was no history of amaurosis fugax, jaw claudication, scalp tenderness, or myalgias. Bilateral cataract extractions had been performed 5 years before presentation; there was also a history of lattice degeneration and dry eye syndrome. The patient denied smoking or alcohol use. The family history was unremarkable for cancer, ocular, or neurologic disease.

On neuro-ophthalmologic examination, the corrected visual acuities were 20/30–2 OD and 20/20+2 OS. Color vision was normal OU. The pupils reacted briskly to light without an afferent defect. Goldmann perimetry was normal OU. There was a moderate right abduction deficit. Maddox rod testing indicated a 10-diopter esotropia in primary gaze that increased to greater than 40 diopters in right gaze. Forced ductions were free. No proptosis or other abnormalities were noted. Mild sensory loss was present to the mid-calves; deep tendon reflexes were diminished symmetrically (1+) throughout.

Magnetic resonance imaging (MRI) of the brain showed an enhancing soft tissue mass at the clivus with involvement of the right cavernous sinus (Fig. 1A). A computed tomography (CT) scan showed bony destruction and anterior extension of tumor into the sphenoid sinus (Fig. 1B). The radiologic differential diagnosis included chordoma, metastatic disease, chondrosarcoma, and plasmacytoma. Thoracic and lumbar spine radiographs showed no evidence of osseous dissemination.

Multiple myeloma and plasmacytoma are rare causes of mass lesions at the skull base and cavernous sinus. Sixth nerve palsy, in isolation or in combination with other cranial neuropathies, may occur rarely as the initial presenting feature of multiple myeloma. We report the neuro-ophthalmologic, radiologic, and pathologic findings for two patients who developed sixth nerve palsies as an initial manifestation of intracranial plasmacytoma and multiple myeloma. One patient presented with an isolated sixth nerve palsy in the setting of multiple vasculopathic risk factors. Treatable skull base lesions, including plasmacytoma and multiple myeloma, must be considered in patients with sixth nerve palsies, especially among those who demonstrate a progressive course or multiple cranial neuropathies.

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graphs showed collapse of the T11 vertebral body (Fig. 1C) with changes suggestive of a lytic process. A skeletal survey indicated involvement of the humeri and femora by lytic lesions; these findings were suspicious for multiple myeloma. Serum protein electrophoresis (SPEP) showed a prominent homogeneous band in the slow-gamma region, reacting on immunofixation as immunoglobulin G (IgG) kappa. The concentration of paraprotein, measured by densitometry, was 0.62 g/dL. A 24-hour urine was positive for Bence-Jones proteins. Bone marrow biopsy showed a modest plasmacytosis with a focal cluster of plasma cells; the degree of plasmacytosis satisfied minor criteria for multiple myeloma.

An endoscopic sphenoidectomy with biopsy of the clivus mass was performed. Light microscopy of the tumor showed uniformly atypical plasma cells (Fig. 2A). Immunoperoxidase staining for immunoglobulin light chains confirmed kappa restriction (Fig. 2B), consistent with plasmacytoma. Treatment was initiated with focal brain radiation therapy, followed by systemic chemotherapy with melphalan and prednisone.

Case 2

A 59-year-old man with a history of chronic obstructive pulmonary disease and hypertension presented with a 2-week history of right occipital pain radiating to the
orbital region. This was accompanied by horizontal diplopia, epistaxis, and difficulty with tongue movements. The pain was dramatically increased by neck extension. There was no ptosis, jaw claudication, or amaurosis fugax. The patient had a 40-pack-year history of smoking. Family history showed lung cancer in the patient's mother, brother, and sister.

Neuro-ophthalmologic examination showed corrected visual acuities of 20/20 OU. He perceived 9/10 HRR color plates correctly OU. Goldmann perimetry showed minimal constriction OU. The pupils were normal. A complete right abduction deficit was present. Alternate cover testing at distance showed a 15-diopter esotropia in primary gaze, which increased to 40 diopters in right gaze. The patient was able to protrude his tongue only minimally, and could not produce horizontal tongue movements to either side.

An MRI of the brain with gadolinium showed an enhancing mass involving the clivus with extension to the right cavernous sinus and sphenoid sinus (Fig. 3). The hypoglossal canals were also involved. Endoscopic sphenoidectomy with biopsy of the tumor showed findings consistent with plasmacytoma. Histopathology of the intracranial tumor was similar to that of patient 1 (Fig. 2). Evaluation for possible multiple myeloma in this patient was negative, including a skeletal survey and bone marrow biopsy. Focal brain radiation therapy was performed.

**DISCUSSION**

Although multiple myeloma commonly involves the nervous system, intracranial involvement is rare (1-4). In 1932, Cushing (5) found that, among 2,000 intracranial tumors, only four cases had multiple myeloma. Clarke (6) has divided cranial myelomas into three groups. In group 1, the tumor involves the skull base and characteristically manifests with cranial nerve palsies. Group 2 tumors are termed "intracranial tumor syndromes," because the myeloma extends into the parenchyma of the
FIG. 3. Patient 2. Axial T1-weighted MR image showing enhancing mass involving the clivus (arrow). The hypoglossal canals, cavernous sinus, and sphenoid sinus also show tumor involvement.

Cranial nerve palsies, particularly sixth nerve paresis, may be initial presenting features of rare but treatable tumors, including plasmacytoma and multiple myeloma. When double vision associated with a sixth nerve palsy progresses beyond 1 week, a compressive cause should be strongly considered and neuroimaging performed.

REFERENCES
Isolated Inferior Rectus Muscle Palsy Resulting From a Nuclear Third Nerve Lesion as the Initial Manifestation of Multiple Sclerosis

Andrew G. Lee, MD, Rosa A. Tang, MD, Gina G. Wong, OD, Jade S. Schiffman, MD, and S. Singh, MD

Isolated inferior rectus muscle (IRM) palsy due to a nuclear or fascicular third nerve lesion is uncommon (1-4), and third cranial nerve palsy as the presenting sign of multiple sclerosis (MS) is rare (5-9). We report an unusual patient with an isolated IRM palsy caused by a demyelinating lesion in the midbrain seen on magnetic resonance imaging (MRI).

CASE REPORT
A 27-year-old woman presented with the acute onset of binocular vertical diplopia on June 20, 1999. She denied any dizziness, vertigo, weakness, or headache. She had no ocular history of trauma or ocular misalignment. Her medical history was significant for anemia, recurrent urinary tract infections, and childhood asthma. Her only medication was an oral contraceptive. Family history was significant for MS in a maternal great aunt.

On examination, her visual acuity was 20/20 OU. The pupils measured 3.5 mm in light and 6 mm in dark bilaterally. There was no relative afferent pupillary defect. Results of automated (Humphrey) visual field tests were normal OU. Slit-lamp biomicroscopy, intraocular pressure measurements, and ophthalmoscopy were normal OU. There was no optic atrophy or optic disc edema. Cutaneous sensation to pinprick in the trigeminal distribution was symmetric and corneal sensation was normal bilaterally. Results of neurologic examination were normal. Extraocular motility examination indicated a moderate underaction of the left IRM. There was a left hypertropia (LHT) of 6 prism diopters (PD) and a 4 PD exotropia (XT) in the primary position. In right gaze, the deviation measured 2 PD LHT and 2 PD XT and in left gaze, 8 PD LHT and 6 XT. In upgaze there was a 4 LHT and 5 XT and in downgaze there was an 8 LHT and 6 XT. In right head tilt, her deviation measured 7 PD LHT and 5 PD exotropia (XT). In left head tilt, the deviation measured 6 PD LHT and 4 PD LXT. There may have been mild fatigue of the left IRM in downgaze.

MRI of the brain showed increased signal intensity on the T2-weighted image measuring approximately 1 to 2 mm within the left dorsal midbrain just ventral to the cerebral aqueduct at the level of the 3rd cranial nerve nucleus (Fig. 1). This lesion was believed to be consistent with demyelination. Additional periventricular areas of increased signal intensity (consistent with demyelination) on T2-weighted and fluid attenuated inversion recovery sequences of the MRI were demonstrated. A lumbar puncture showed normal cell count, protein, and glucose, but there were two oligoclonal bands present and an increased immunoglobulin G (IgG) synthesis rate. Serum antinuclear antibody, erythrocyte sedimentation rate, anti-cardiolipin antibodies, lupus anticoagulant, thyroid function tests, and vitamin B12 level were normal. Visual evoked responses were normal bilaterally. She was treated with a 5-day course of intravenous methylprednisolone (1,000 mg/d). Four days after completing her steroids, she experienced resolution of her diplopia. On August 30, 1999, she had a small 3 PD left hyperphoria in primary position but no diplopia, and on February 3, 2000 (8 months later), she had only a small residual asymptomatic (1 PD) left hyperphoria.

DISCUSSION
Isolated extraocular muscle involvement caused by a nuclear third cranial nerve palsy is rare (1-5). The differential diagnosis of an isolated IRM palsy includes orbital lesion (e.g., orbital pseudotumor, tumor, traumatic or postsurgical restrictive disease, thyroid ophthalmopathy); neuromuscular junction lesion (e.g., myasthenia gravis); and partial third nerve palsy. Although uncommon, brainstem lesions can cause and isolated IRM palsy. Harrison and Wirtschafter (10) reported an isolated, unilateral IRM paresis occurring in a patient with a mesencephalic tegmental cavernous angiomma. Chou and Demer (11) reported a case of isolated IRM palsy secondary to a breast cancer metastasis to the oculomotor nucleus.
The nucleus of the third cranial nerve is composed of various subnuclei. The eyelids (levatorators) are innervated bilaterally by a single central caudate nucleus. The Edinger-Westphal nuclei innervate the pupils. The extraocular muscles (i.e., superior rectus, inferior rectus, inferior oblique, and medial rectus) are served by individual subnuclei. The innervation of the subnuclei is ipsilateral to the respective extracranial muscles except for the superior rectus (innervated by the contralateral subnucleus). The medial rectus subnucleus is quite large, and isolated medial rectus paresis caused by a nuclear lesion is unusual. Thus, nuclear third cranial nerve palsies may present in any of the following ways:

1. Unilateral third nerve palsy with contralateral superior rectus palsy and bilateral ptosis (single caudate nucleus)
2. Bilateral third nerve palsy with no ptosis (sparring of single caudate nucleus)
3. Complete bilateral third nerve palsy
4. Bilateral ptosis alone (but not unilateral ptosis)
5. Isolated weakness of one muscle innervated by the third nerve (except perhaps the medial rectus muscle)

Our patient presented with an isolated left IRM weakness caused by a lesion in the area of the third nerve nucleus. A lesion of the fascicle of the third nerve can not be completely excluded. This lesion was shown on MRI of the dorsal midbrain. The patient had other signs of demyelinating disease, including oligoclonal bands in the cerebrospinal fluid and other periventricular white matter lesions. A presumptive diagnosis of probable MS was made in this patient.

Although ocular symptoms occur in up to 83% of patients with MS, isolated cranial nerve palsy as the presenting manifestation of MS is uncommon (5-9). The typical presenting ocular sign of MS is usually optic neuritis. Isolated cranial nerve palsy, however, may be the initial manifestation in up to 5.2% of patients. Thorneke et al. (7) reported 14 patients with definite MS with isolated ocular motor cranial nerve palsies (one third nerve palsy, one fourth nerve palsy, and 12 sixth nerve palsies). Newman and Lessell (5) reported an isolated pupil-spared third nerve palsy in MS. Uitti and Rajput (6) described a pupil-involved third nerve palsy as the presenting sign of MS. Książek et al. (4) described two superior division third nerve palsies and one inferior branch palsy due to intrinsic extra-axial midbrain lesions, one of whom had MS. Rush and Young (9) in a large retrospective series reported that only 2.75% of third nerve palsies were attributable to MS.

Patients with MS and diplopia usually have a sixth nerve palsy or an internuclear ophthalmoplegia. These patients also may have saccadic abnormalities and acquired nystagmus. Clinicians should be aware that IRM palsy may be caused by a nuclear midbrain lesion and, although rare, this may be the presenting manifestation of MS.

Acknowledgement: This work was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc., New York, NY.

REFERENCES
Unilateral Adie Pupil as Sole Ophthalmic Sign of Anti-Hu Paraneoplastic Syndrome

Michiko Kimura Bruno, MD, Jacqueline M.S. Winterkorn, PhD, MD, Mark A. Edgar, MD, Ayeesha Kamal, MD, and J. Patrick Stiibgen, MD

Unilateral Adie pupil is usually a benign finding. The authors report the case of a 73-year-old man in whom pupillary abnormality was accompanied by areflexia, generalized sensorimotor neuropathy, and autonomic dysfunction. Anti-Hu antibody associated with small cell lung cancer was found in the serum and cerebrospinal fluid. Unilateral Adie pupil was the sole ophthalmic manifestation of anti-Hu syndrome. A variety of ophthalmic signs can signal paraneoplastic syndromes, most commonly ophthalmopareses, opsoclonus-myoclonus syndrome, cancer-associated retinopathy, or optic neuropathy. The authors present a case in which a unilateral Adie pupil was the sole ophthalmic manifestation of anti-Hu syndrome.

CASE REPORT

A 73-year-old man noticed blurry vision OD while reading. When he looked in a mirror, he saw that his right pupil was dilated. During the following weeks, he was bothered by bright lights. About 3 months earlier, he had developed generalized malaise and a dry cough. Shortly thereafter, he noticed discomfort and numbness in both feet, as if he were walking on a "cushion of air." As the numbness ascended to his ankles, he developed difficulty walking. He then started to experience pins-and-needles sensations and numbness in his fingers. He complained of dry mouth and noted dizziness when he stood up. Family members described that the patient sweated profusely while eating hot food. He was a heavy smoker and a social drinker. His medical history was significant for a myocardial infarction and bypass surgery.

Visual acuity was 20/30 OU, visual fields were full, and eye movements were intact, with smooth pursuit, brisk saccades, and no ptosis or nystagmus. The fundus appeared normal. The right pupil was mydriatic, 8 mm in diameter, and showed neither direct nor consensual constriction to light. The right pupil did not constrict on attempted accommodation. The left pupil was 4.5 mm in diameter and constricted to near and to light shown in either eye, without afferent pupillary defect. Forty minutes after instillation of a drop of dilute pilocarpine 0.1% OU, the right pupil had constricted to 1.0 mm, whereas the left pupil diameter remained 4.5 mm.

The patient's general examination was remarkable only for orthostatic hypotension, with blood pressure dropping from 170/100 mm Hg supine to 100/60 mm Hg sitting, without change in pulse rate. On neurologic examination, his cognitive function was normal. He had loss of all modalities of somatic sensation distally in all four extremities. His coordination was impaired. He was areflexic and distally weak, and he had flexor response of the toes. Gait was wide-based and unsteady.

Magnetic resonance imaging (MRI) of the head, cervical spine, and lumbar spine was within normal limits. Results of blood tests were normal, including complete blood count, chemistries, vitamin B12, folate, angiotensin-converting enzyme, thyroid function tests, and acetylcholine receptor antibodies. Serum Lambert-Eaton Myasthenic syndrome (LEMS) antibody was negative. Nerve conduction studies showed an axonal sensorimotor polyneuropathy. There was no incremental response to repetitive stimulation. Biopsy of the sural nerve showed no significant changes with hematoxylin and eosin (H&E) staining, but electron microscopy showed changes consistent with severe axonopathy (Fig. 1). Cerebrospinal fluid contained protein of 105 mg/dl and glucose of 69 mg/dl. Anti-Hu antibody titers were positive in both cerebrospinal fluid and serum. Computed tomography (CT) of the chest showed a 0.8-cm nodule in the left upper lobe of the lung, and biopsy of a mediastinal lymph node confirmed small cell lung carcinoma.

DISCUSSION

Anti-Hu antibodies in serum or CSF have been associated with a wide spectrum of neurologic disorders, including brainstem and limbic encephalomyelitis, cerebellar degeneration, sensory and motor neuropathies, autonomic dysfunction, and visual loss. Neuro-ophtalmologic presentations of anti-Hu antibody syndrome can be prominent (1) and include ophthalmopareses, nystagmus, and opsoclonus-myoclonus, which is usually asso-
Unilateral Adie Pupil as Sole Ophthalmic Sign of Anti-Hu Paraneoplastic Syndrome

An elderly patient with a unilateral Adie pupil was diagnosed with anti-Hu paraneoplastic syndrome. The patient presented with unilateral mydriasis, tonic pupils, and myasthenic syndrome. Full neurologic examination and an appropriate workup are warranted in such cases.

REFERENCES

Retinol-Binding Protein in Idiopathic Intracranial Hypertension (IIH)

John B. Selhorst, MD, Kongkiat Kulkantrakorn, MD, James J. Corbett, MD, Enrique C. Leira, MD, and Sophia M. Chung, MD

Objective: We postulated that an alteration in endogenous vitamin A (retinol) metabolism plays a causal role in the pathogenesis of idiopathic intracranial hypertension (IIH).

Materials and Methods: Serum retinol was determined by a fluorometric method from 40 control subjects and 58 patients with idiopathic intracranial hypertension (IIH). Retinol binding protein (RBP) was also assayed by quantitative radial immunodiffusion in 17 control subjects and 30 patients with IIH.

Results: Mean retinol values were higher in the IIH group compared with the control group, but did not reach a significant level. However, seven of 30 patients with IIH had high RBP levels, but none of the control subjects did.

Conclusion: This data suggests that IIH is associated with an abnormality in vitamin A metabolism that is linked to its transport system.

Key words: Idiopathic intracranial hypertension—Obesity—Pseudotumor cerebri—Retinol-binding protein—Vitamin A.

Idiopathic intracranial hypertension (IIH) is a syndrome of headaches, papilledema, and elevated intracranial pressure without evidence of an intracranial mass lesion or meningeal inflammation (1,2). This condition is also known as pseudotumor cerebri or benign intracranial hypertension. A disorder of metabolism occurring in IIH is suggested by the common features of obesity in young adult females (2). IIH is reported with a host of drugs and medical conditions, but these observations are retrospective, are very infrequent, and likely are due to chance (3). Interestingly, IIH is more predictably induced by excessive intake of vitamin A in the diet or by supplementary ingestion (4–7). Little is known, however, about the endogenous metabolism of this vitamin in patients with IIH. Therefore, a study to define an association of serum vitamin A (retinol) and retinol-binding protein (RBP) levels was undertaken to determine whether an alteration in vitamin A metabolism or its transport played a causal role in the pathogenesis of IIH.

METHODS

Patients with IIH had normal neurologic examinations, neuroimaging studies, and spinal fluid analysis except for papilledema and elevated intracranial pressure. The protocol was approved by the institutional review boards of the participating institutions to obtain serum samples from all consenting participants in this study. Subjects in the control and IIH groups had no history of excessive vitamin A intake in their diets, ingestion of vitamin supplements, oral contraceptive tablets, or supplemental hormones. Serum samples were prospectively collected at two academic medical centers (Saint Louis University and University of Iowa). Serum vitamin A was assayed in 40 healthy control subjects and 58 patients with IIH as described by Thompson et al (8). Serum RBP was measured in samples from 17 control subjects and 30 patients by a quantitative radial immunodiffusion (M-partigen immunodiffusion plate plasma retinol-binding protein, Calbiochem Behring Corp., La Jolla, CA).

RESULTS

In both control and IIH groups, there was no significant difference regarding sex, age, or height. The mean weight in the IIH group, however, was significantly higher than in the control group (P < 0.001, Student's t-test) (Table 1). The mean retinol level in the IIH patients was higher than in the control group (60.0 ± 20.1 [SD] versus 51.3 ± 19.0 µg/dl), but did not reach a significant level (P = 0.06). Nineteen of 58 patients in the IIH group had a high vitamin A level, whereas 9 of the 40 subjects in the control group did (odds ratio, 1.68; 95%CI, 0.38–7.34) (Table 2). The mean RBP level in the IIH patients was significantly higher than in the control group (4.1 ± 1.7 versus 2.8 ± 1.1 mg/dl, P = 0.008). Seven of 30 patients in the IIH group had high RBP levels, whereas none of the 17...
subjects in the control group did (odd ratio, 10.35; 95% CI, 4.61–23.92) (Table 2). All of the elevated RBP samples, however, were from one investigative site that provided 17 of 58 samples.

DISCUSSION

The pathophysiology of IIH is attributed to excess cerebrospinal fluid (CSF) production, diffuse cerebral edema, or decreased CSF absorption by arachnoid villi (9,10). The latter mechanism is favored by reports that show increased resistance to CSF absorption and decreased clearance of isotope-labeled CSF over the vertex (11–13). The pathogenesis of the impaired CSF absorption remains undetermined. Fibrosis of arachnoid villi has been found in animal studies of hypovitaminosis (14), but these changes do not occur with excess vitamin A (15). Vitamin A is essential for the proliferation and differentiation of cells throughout the body (16). This dynamic activity and the sensitivity of the arachnoid villi to deficient levels of vitamin A suggests a possible linkage between dysfunction of the subarachnoid villi and high levels of vitamin A or its metabolites.

Normally, most of the body’s total vitamin A is stored in the stellate cells of the liver and within lipid droplets of hepatocytes. Interestingly, excess vitamin A may be stored in adipose tissue (17). Therefore, obese patients, as in IIH, would have added capacity for vitamin A storage and, thereby, excess vitamin A for recycling throughout the body. RBP provides the principal transport mechanism for this fat-soluble vitamin between natural storage sites and cellular tissues throughout the body (17). In animals, plasma levels fall in vitamin A-deficient states and rise with injection of vitamin A into deficient animals (18). Hence, assays of RBP in humans may reflect the activity of vitamin A transport in the bloodstream. Interestingly, estrogen and progesterone influence RBP production, and several drugs are known to affect the absorption, binding, storage, or transport of vitamin A (19–21). Perhaps the many drugs reportedly associated with IIH act on vitamin A transport (21).

In this study, approximately one third of IIH patients had high vitamin A levels, compared with approximately one fourth of the control subjects, but the mean levels in each group were not significantly different. Interestingly, despite a similar overlap in a report of 70 controls and 16 patients with IIH, Jacobson and associates (22) recently found a statistically significant difference between elevated serum vitamin A. Because of the active storage and transport of this fat-soluble vitamin, serum RBP determinations are only an indirect measure of total body vitamin A metabolism. Therefore, these inconclusive serum retinol assays do not negate the possibility of an endogenous excess of vitamin A in patients with IIH.

The elevated RBP determinations found in patients with IIH in this study were especially intriguing. Importantly, none of the control subjects had elevated RBP levels. These results suggest an active vitamin A transport in patients with IIH. Unbound vitamin A has a toxic effect on cells, but binding to RBP prevents this injury (20,23). With an increase in vitamin A transport, cells with RBP receptors would receive an excess of vitamin A (17). Excessive transport of vitamin A to the arachnoid villi could possibly result in their malfunction, produce added resistance to CSF absorption, and raise intracranial pressure. Therefore, a chronic increase in vitamin A within arachnoid villi would be the principal pathogenetic mechanism in IIH. These results warrant further investigation of vitamin A and its metabolites in patients with IIH, perhaps to include assays in fat, spinal fluid, and liver.

Acknowledgements: The authors are most grateful to Dr. Frank Chytil for his very useful suggestions in preparing this report and the assistance of his biochemistry laboratory at Vanderbilt University in determining levels of serum retinol and RBP. We also appreciate the effort of Mary Althage with this manuscript.

REFERENCES


TABLE 1. Clinical features

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<td>95.1 ± 26.8*</td>
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<td>Height in cm (mean)</td>
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* P < 0.001. IIH, idiopathic intracranial hypertension.

TABLE 2. Subjects’ retinol and RBP levels

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* Trend not significant; † Significant, see results. RBP, retinol-binding protein.
Giant Cavernous Carotid Aneurysms: Clinical Presentation in Fifty-seven Cases

Cecil D. Hahn, MD, David A. Nicolle, MB, ChB, FRCSC, FRCSE, FRCOphth, Stephen P. Lownie, MD, FRCSC, and Charles G. Drake, MD, FRCSC

Objectives: To review the presenting symptoms and ophthalmic findings of 57 patients with cavernous carotid aneurysms of giant size (>2.5-cm diameter).

Materials and Methods: Hospital charts of 57 patients with giant cavernous carotid aneurysms who presented to University Hospital in London, Ontario, Canada between 1961 and 1993 were reviewed. All patients were proven by cerebral angiography to have unruptured giant cavernous carotid aneurysms.

Results: Forty-six patients (81%) were women (mean age, 54 years). The most common presenting symptoms were diplopia (89%), retroorbital pain (61%), headache (19%), diminished or blurred vision (14%), and photophobia (4%). The most common clinical sign was partial or complete ophthalmoplegia (93%). Trigeminal nerve involvement was found in 37% of patients. Other clinical signs included ptosis, decreased visual acuity, proptosis, and visual field defects.

Conclusions: This study characterizes a large group of patients with giant cavernous carotid aneurysms seen over a 30-year period at a single institution. As in previous studies, diplopia and retroorbital pain were the most common symptoms. The high incidence of ophthalmoplegia observed in this study may be explained by a greater compressive and/or ischemic effect of giant aneurysms compared with their smaller counterparts.

Key Words: Carotid artery diseases—Cerebral aneurysm—Internal carotid artery—Cavernous sinus—Ophthalmoplegia—Case series—Retrospective studies.
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<td>Selverstone clamp</td>
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* Sensory and/or motor involvement of cranial nerve five.
O Partial paresis of cranial nerves three, four, and six.
< Partial paralysis of cranial nerves three, four, and six.
V, trigeminal nerve divisions one (V,), two (V), and three (V); III, cranial nerve three; IV, cranial nerve four; VI, cranial nerve six; VA, visual acuity; EC-IC, extracranial-intracranial bypass; ICA, internal carotid artery; RAPD, relative afferent pupillary defect.

**RESULTS**

Complete results are summarized in Table 2.

**Patient Characteristics**

Of the 57 patients with giant cavernous carotid aneurysms, 46 patients (81%) were women and 11 patients (19%) were men (mean age, 54 years). The youngest patient was a 6-year-old boy, and the oldest patient was a 74-year-old woman. The most commonly seen group was middle-aged to elderly women. In the pediatric population (patients younger than 18 years), all four patients were male.

**Presenting Symptoms**

The most common presenting symptom was diplopia, seen in 51 patients (89%). Retroorbital pain was reported by 35 patients (61%). Headache (defined as pain that was not specifically retroorbital) was reported by 11 patients (19%). Diminished or blurred vision was reported by eight patients (14%), and photophobia was reported by two patients (4%).

**Clinical Signs at Presentation**

The most common clinical sign at presentation was ophthalmoplegia, which was seen in 53 patients (93%), of which 44 (77%) had partial ophthalmoplegia and nine...
Combined paresis of cranial nerves three, four, and six was present in 22 patients (39%). No patient demonstrated combined involvement of cranial nerves four and six alone. Isolated third cranial nerve paresis was present in six patients (11%), and isolated sixth cranial nerve paresis in 13 patients (23%). Combined paresis of cranial nerves three and four was seen in 13 patients (23%). Combined paresis of cranial nerves three and six alone was seen in 11 patients (19%). Combined paresis of cranial nerves four and six alone was seen in one patient (2%). No patients demonstrated combined involvement of cranial nerves four and six alone. Ophthalmoplegia was the second most common presenting sign, present in 51% of patients. Ptosis was a presenting sign in 29 patients (51%), and decreased visual acuity was seen in seven patients (12%). Propothesis was present in four patients (7%), and visual field defects were found in four patients (7%).

**DISCUSSION**

Several previous studies (6,7,8) documented the clinical presentation of cavernous carotid aneurysms of mixed size, and one study focused on cavernous carotid aneurysms of giant size (9). To our knowledge, the current study represents one of the largest reported series of patients with giant cavernous carotid aneurysms. These patients were seen in a single institution, which permitted comprehensive selection of patients and systematic analysis of clinical records.

The patients reviewed in this study represent a highly select group, many of whom were referred to this center because of its expertise in the treatment of giant aneurysms. Most patients sought treatment at a time when noninvasive neuroimaging techniques, including computed tomography (CT) and magnetic resonance imaging (MRI), were not yet available. As a result, all patients in this study were symptomatic at presentation, in contrast to other case series that have included asymptomatic patients whose cavernous carotid aneurysms were identified incidentally by CT or MRI.

We used caution when comparing this study to previous case series of cavernous carotid aneurysms because each series differs in its method of patient selection and in its definition of clinical symptoms (such as “headache” versus “retroorbital pain”). The characteristics of our patient group were very similar to those reported in previous case series. The great majority of our patients (81%) were women, and the mean age for both sexes was 54 years; these statistics are in agreement with previously reported associations of cavernous carotid aneurysms with women and advancing age (6,8,10).

We summarized our patients' signs and symptoms by specific categories to facilitate comparison with other studies. Diplopia and retroorbital pain were by far the most common presenting symptoms in our patient group. Ophthalmoplegia was by far the most common presenting sign; it was present in 93% of our patients. Ophthalmoplegia was more commonly partial than complete, and in agreement with previous observations (6), cranial nerve six was most commonly involved (81%), followed by cranial nerves three (54%) and four (23%). Ptosis was the second most common sign, present in 51% of patients.

### TABLE 2. Summary of presenting signs and symptoms

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>No. patients</th>
<th>%</th>
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<td>81</td>
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<td>M</td>
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<td>Presenting symptoms</td>
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<td>Motor paralysis</td>
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The trigeminal nerve was affected in 21 patients (37%). The ophthalmic division (V,) was involved in 19 patients (33%), the maxillary division (V,) in 15 patients (26%), and the mandibular division (V,) in six patients (11%). The most common sensory abnormality was hypalgesia or analgesia (decreased or absent pain sensation). On occasion, neuralgia (unprovoked pain sensation) and paresthesia (abnormal sensation) were also seen in various branches of the trigeminal nerve distribution. Paralysis of the muscles of mastication (V,) was present in two patients (4%).

We used caution when comparing this study to previous case series of cavernous carotid aneurysms because each series differs in its method of patient selection and in its definition of clinical symptoms (such as “headache” versus “retroorbital pain”). The characteristics of our patient group were very similar to those reported in previous case series. The great majority of our patients (81%) were women, and the mean age for both sexes was 54 years; these statistics are in agreement with previously reported associations of cavernous carotid aneurysms with women and with advancing age (6,8,10).
A possible correlation between the size of cavernous carotid aneurysms and the severity of their clinical presentation has been a matter of debate. Linskey et al. (6), in a study of 37 patients with mixed-size cavernous carotid aneurysms, reported no correlation between aneurysm size and the severity of symptoms. However, Kupersmith et al. (7), in a study of 70 patients with mixed-size cavernous carotid aneurysms, found that only patients with aneurysms of giant size presented with ophthalmoplegia. We found that our patients with giant aneurysms had a higher incidence of ophthalmoplegia (93%) than was reported in previous studies of mixed-size aneurysms. This observation supports the hypothesis that giant aneurysms may cause more symptoms than their smaller counterparts, possibly due to a greater ischemic and/or greater compressive effect on cranial nerves traversing the cavernous sinus (11,12).

The treatment of giant cavernous carotid aneurysms has evolved considerably since the first patients in this study were seen (13,14,15). Traditionally, the treatment of cavernous carotid aneurysms was controlled occlusion of the internal carotid artery in the neck. In the early 1900s, this was accomplished by ligature or by fascial bands; since the 1950s, this was accomplished with metallic clamps designed by Crutchfield and Selverstone (16,17). In some cases, extracranial-to-intracranial bypass surgery was undertaken to augment the cerebral collateral circulation (5). In the 1960s, the use of balloon-mounted catheters began, and by the late 1970s, detachable balloons of silicone or latex had been developed (1,18). Rapid advances in endovascular treatment over the past 10 years have opened up further options for the treatment of these aneurysms, including detachable platinum coils (19).

All of the patients described in this study were treated using ligation, Selverstone clamping, or balloon occlusion of the proximal internal carotid artery, combined at times with extracranial-intracranial bypass. We are unable to comment on the clinical outcomes of these patients because most were referred to this center for treat-
ment and were subsequently followed elsewhere. However, a survey of postoperative clinical notes indicates that many patients experienced immediate improvement in their symptoms after surgical treatment.

Recent studies (4,7) demonstrated the benign natural history of these aneurysms and have argued for a more conservative approach to their treatment. Treatment is now commonly reserved for patients with intolerable pain, progressive ophthalmoplegia or visual loss, evidence of intradural extension or radiographic enlargement, and subarachnoid hemorrhage or epistaxis.

To our knowledge, this study represents one of the largest reported series of patients, seen over a 30-year period in a single institution, with giant cavernous carotid aneurysms. The characteristics of our patient group were similar to those reported in previous case series of cavernous carotid aneurysms, as the majority of our patients were women of an advanced age. As in previous case series, diplopia and unilateral retroorbital pain were the most common presenting symptoms. Ophthalmoplegia was seen in 93% of patients; it most commonly involved the sixth cranial nerve, and it less commonly involved the third and fourth cranial nerves. This high incidence of ophthalmoplegia in patients with giant aneurysms supports the hypothesis that giant aneurysms may cause more symptoms than their smaller counterparts, either by greater compressive or greater ischemic effects on the surrounding cranial nerves.

Acknowledgement: This paper is dedicated to the memory of Charles G. Drake, whose pioneering work on the management of giant intracranial aneurysms contributed greatly to their successful treatment.

REFERENCES

Pneumosinus Dilatans of the Sphenoid Sinus Presenting With Visual Loss

Craig A. Skolnick, MD, Mahmood F. Mafee, MD, and James A. Goodwin, MD

Objective: To report 3 cases of pneumosinus dilatans of the sphenoid sinus associated with visual loss.

Materials and Methods: Retrospective case series describing history of visual loss, visual examination, visual field deficits, and radiologic imaging.

Results: Three patients developed visual loss associated with pneumosinus dilatans of the sphenoid sinus.

Conclusions: Pneumosinus dilatans of the sphenoid sinus is a rare disorder that should be considered in patients presenting with unexplained visual loss.

Key Words: Optic neuropathy—Pneumosinus dilatans—Sphenoid sinus.

Pneumosinus dilatans is a rare condition in which dilated paranasal sinuses lined by normal mucosa are filled with air. Classically, there is no overlying osseous hypertrophy or destruction of bone. The frontal sinus is the most commonly affected, but the sphenoid sinus is the most important for visual loss because of its intimate relation with the optic nerve in the optic canal. This report concerns three patients with visual symptoms and sphenoidal pneumosinus dilatans.

CASE REPORTS

Case 1
A 48-year-old African-American woman had gradual painless loss of vision OD over 6 months. She has had diffuse, nonlocalizing headaches for 3 years, occasionally associated with nausea. There is no history of trauma. She has euthyroid thyrotoxicosis, hyperparathyroidism, early menopause, and Zollinger-Ellison syndrome with severe peptic ulcer disease. She has had yearly prolactin levels and thyroid function tests, the results of which have been normal. Her visual acuity was hand motions OD and 20/20 OS, with a relative afferent pupillary defect OD. Goldmann visual field testing OD showed a large absolute nasal and central defect. The visual field was normal OS. Fundus examination showed temporal pallor and increased cupping of the right optic disc and normal left optic disc. Computed tomography (CT) showed dehiscence of both optic canals (right greater than left), with the intracanalicular portion of the right optic nerve seen in close contact with the air (Fig. 1A). Magnetic resonance imaging (MRI) with gadolinium contrast showed extensive pneumatization of the sphenoid bone extending toward the right optic canal with an area of air intensity adjacent to the right optic nerve (Fig. 1B).

Case 2
A 26-year-old Hispanic woman with rhinitis had immediate loss of the upper field of vision OD after blowing her nose. There was some recovery of visual field after an hour, leaving a permanent nasal scotoma that respected the horizontal midline and extended nearly to the physiologic blind spot (Fig. 2). The visual field was normal OS. She experienced some transient flashing pink lights in the part of the upper field that recovered. She denies trauma or headaches. Visual acuity was 20/25 OD and 20/15 OS, with no relative afferent pupillary defect. Examination 2 years after presentation showed sectoral pallor of the inferotemporal optic disc with corresponding loss of nerve fiber layer striations. Examination 1 year after onset had not shown these findings. MRI with gadolinium contrast showed pneumatization of the sphenoid sinus and posterior ethmoid cells adjacent to the optic canal. CT of the orbits showed an area of bony dehiscence between the right posterior ethmoid air cell and the floor of the optic canal. This bony wall was intact on the left side (Fig. 3).

Case 3
A 25-year-old white man had eight episodes of transient visual loss OS over a 6-month period. A typical episode began with a patchy central and peripheral darkness that progressed over 2 minutes, leaving a small central island, which then closed completely, at which time the eye had no light perception. This lasted approximately 15 minutes, followed by gradual opening in a
patchy fashion. He denied any particular activity, event, or posture temporally related to the attacks. There has never been pain or headache associated with the attacks, but occasionally he has had a steady pressure over his temples and behind his eyes. Visual acuity was 20/15 OU without afferent pupillary defect. Results of Goldmann visual fields and fundus examination were normal OU. Work-up for collagen-vascular disease indicated an elevated anti-Smith antibody. CT showed extensive pneumatization of the sphenoid bone with extension into the lesser wing of the sphenoid and anterior clinoid adjacent to the left optic canal (Fig. 4). Part of the optic canal was dehiscent, and the optic nerve appeared to be in close contact with the air space.

**DISCUSSION**

Frontal pneumosinus dilatans was first fully described by Benjamin in 1918 (1). Lombardi et al. (2) reviewed the literature in 1967 and found 51 cases, with 39 involving the frontal sinus and only five involving the spheno-ethmoidal sinus. Most patients were male (48 of 51), and most were between 20 and 40 years of age. The presentation depends on the sinus affected. Frontal sinus involvement may produce localized tenderness or variable proptosis secondary to orbital communication. Complaints may include headache and visual disturbances such as decreased visual acuity, bitemporal hemianopia, and diplopia secondary to motility disorder. The
The stimulus for pneumatization of the paranasal sinuses rapidly to their adult size. There is a wide variability in Sinuses grow slowly until puberty, after which they grow placement of cancellous bone, forming compact bone. plates, and the greater and lesser wings of the sphenoid sum sella, the clivus, the clinoid processes, pterygoid recesses of the frontal sinuses, the superior recess of the maxillary sinus, the sellar region in the sphen-ethmoidal sinusises, and the orbit with anterior ethmoidal involvement.

During development, ethmoid sinus cells expand within the ethmoid box, leading to compression and displacement of cancellous bone, forming compact bone. The stimulus for pneumatization of the paranasal sinuses is thought to be growth of the mucosal lining into bone. Sinuses grow slowly until puberty, after which they grow rapidly to their adult size. There is a wide variability in "normal pneumatization" of the paranasal sinuses, with the sphenoid sinus showing the most variability. Pneumatization of the sphenoid sinus may occur in the dor-sum sella, the clivus, the clinoid processes, pterygoid plates, and the greater and lesser wings of the sphenoid bone. Simple aeration of the anterior clinoid without enlargement of bulging is a normal variant, occurring in 13% of the population (3). Explanation for sinus dilatation remains speculative. Suggestions have included congenital abnormality, inflammation (4), and a valve-like obstructive mechanism of the sinus (5). Pneumosinus dilatans may be static for some time, and then overgrowth may rapidly occur.

Pneumosinus dilatans has been associated with meningioma and fibro-osseous disease. Lloyd (6) described six cases presenting with proptosis, three of which had meningioma associated with fronto-ethmoid sinus dilatation. Two patients with fibrous dysplasia had maxillary antral dilatation, and one patient with an ossifying fibroma of the posterior orbit had fronto-ethmoidal sinus dilatation. Wiggli and Oberson (7) reported seven patients with anterior chiasmatic angle meningiomas associated with sphen-ethmoid dilatation with variable degrees of hyperostosis. This same relationship has been reported without overlying hyperostosis (8). Hirst et al. (4) have reported three cases of sphenoidal pneumosinus dilatans associated with intracanicular meningiomas of the optic nerve sheath without adjacent hyperostosis. Two of these cases had bilateral meningiomas. Spoor et al. (9) described a case of pneumosinus dilatans of the frontal and sphenoid sinuses in combination with Klippel-Trenaunay-Weber syndrome (port-wine hemangio­mas, deep venous abnormalities, and soft tissue and bony hypertrophy) and familial Adie’s pupil who developed bilateral optic nerve sheath meningiomas. Patients with sphenoidal pneumosinus dilatans and unexplained progressive visual loss may have occult meningiomas of the optic nerve sheath missed with standard neuroimaging.

Pneumosinus dilatans without an associated pathologic process rarely causes visual loss. A total of 11 cases have been previously reported in the literature (2,5,10-16). Two patients underwent craniotomy, and two under­went sphenoid sinus decompression. Sugita et al. (5) described a young man with multiple episodes of transient bilateral complete blindness, occurring while driving up a mountain or after take-off in an airplane. His visual acuity at presentation was counting fingers OD and 20/30 OS, and tomograms suggested bone defects in the sphenoid sinus around the optic canals. The attack was inductive in a hyperbaric chamber when the atmospheric pressure was lowered. The patient underwent sphenoid sinus decompression via trans-maxillary sinusotomy. Postoperatively, the patient’s visual acuity improved to 20/70 OD and 20/20 OS, and he did not have a recurrent episode of transient blindness, even when rechallenged in the hyperbaric chamber. The authors speculated that air inside an abnormally large sphenoid sinus can expand under decreased atmospheric pressure and push the optic nerve through a bony defect, thus causing a disturbance of the regional blood flow.

Approximately 1 mm of optic canal wall separates the optic nerve from the sinus cavity. Excessive pneumatization can lead to thinning and gross dehiscence of the canal wall. The optic nerve is bound within the dural sheath and is relatively immobile and susceptible to local forces. Radiographic (CT) studies of patients with inflammatory sinus disease and suspected optic nerve disease have shown up to 3% of optic nerves contact or protrude slightly into the posterior ethmoid air cells (17,18), and the optic canal traverses or bulges into the sphenoid sinus in 6% to 8% of patients (18,19). The frequency of dehiscent bone between the sphenoid sinus and the optic nerve is 4% in two independent cadaveric studies (20,21). CT studies have shown up to a 24% incidence of optic canal bony dehiscence as defined by absence of bone density along the medial wall of the optic canal (18). Differences in frequency may be attributable to inability to visually discern bone thickness less than 0.5 mm on a CT examination. The presence of anterior clinoid pneumatization increases the likelihood of optic nerve exposure and canal dehiscence (18).

The mechanism leading to optic neuropathy is uncertain. With direct communication between the sinus and the optic canal, one could postulate a direct compressive effect by mucosa or air leading to ischemic damage.
Upward displacement of both the pituitary fossa and planum sphenoidale with distortion of the tuberculum sellae may cause direct compression of the optic chiasm or interfere with chiasmal circulation in patients who present with bitemporal visual field defects (22). Three of 11 previously reported cases had this radiologic finding (2,13,15).

None of the three cases presented here underwent surgical decompression. It is possible that an occult meningioma of the optic nerve sheath exists in these patients. Patients with unexplained optic atrophy and normal neuroimaging should be followed-up as meningioma suspects. Patients should receive periodic CT and MRI, with special attention to the optic canals and sellar region.

These cases represent the association of a specific radiographic finding with three different clinical presentations. Because of the small number of cases and varying subjective and objective data, it is difficult to clinically characterize sphenoidal pneumosinus dilatans. Although cases 1 and 2 displayed optic neuropathy, one cannot definitely determine the cause to be pneumosinus dilatans. Case 2 did not have a detectable relative afferent pupillary defect on examination. It is possible that the disparity in optic nerve function was not detectable, because the total area of affected visual field was small. Videopupillography was not available when this patient initially presented. Case 3 lacks objective evidence of optic nerve disease. This patient may in fact be having a variant of visual migraine; however, the association of his exclusively left eye symptoms and pneumosinus dilatans on the same side is compelling.

Because this is a rare disorder, it is not clear how to manage these patients. It has been suggested that sudden elevation of the intrasinus pressure as with sneezing or with altitude change may cause direct damage to an exposed optic nerve. Our second patient (case 2) is a dramatic example of this mechanism, and for her, surgical options aimed at preventing future attacks or progressive optic neuropathy must be considered. These would include creating an outlet for decompression from the sphenoid into the maxillary sinus (transmaxillary sinusotony), enucleating the sinus to remove the mucosal lining (because it is thought to be the stimulus for pneumatization [12]), or packing the sinus with fat to tamponade a bony dehiscence in the optic canal.

REFERENCES


A patient with diplopia had a carotid cavernous fistula associated with a persistent primitive trigeminal artery that was seen with angiography. Balloon occlusion of the carotid cavernous fistula resulted in flow stasis of the persistent primitive trigeminal artery and resolution of the symptoms. Persistent primitive trigeminal artery may be associated with a carotid cavernous fistula.

**Key Words:** Carotid—Fistula—Primitive vessels.

We present a case of persistent primitive trigeminal artery (PPTA) associated with a carotid cavernous fistula (CCF). Persistent primitive trigeminal artery is the most common remnant of the embryologic cerebral vascular system. The trigeminal artery is usually present for 7 days of fetal development and serves as an anastomosis between the carotid and vertebral systems. A PPTA was first described in 1844 by Quain (1). The first PPTA was diagnosed radiographically in 1950 by Sutton (2). Only 0.1% to 0.6% of cerebral angiograms show a PPTA. There is a 25% incidence of other associated cerebral vascular abnormalities with a PPTA (3,4,5). The presence of this congenital anomaly may predispose development of a traumatic cavernous sinus fistula despite trivial trauma.

**CASE REPORT**

An 83-year-old woman presented after a high-speed motor vehicle accident. She was confused but hemodynamically stable. Results of computed tomography of the head were negative. Twenty-four hours later, the patient experienced diplopia. Results of ophthalmologic evaluation showed cranial nerve deficits of nerves III (partial), IV, V, and VI, and it showed Horner syndrome OD. Corneal sensation was decreased OD. Initially, there was minimal proptosis and injection of the eye; however, these signs increased over the ensuing days. Visual acuity and intraocular pressures remained normal and equal bilaterally. There was no evidence of facial trauma.

Results of a repeated computed tomography scan of the head showed subtle soft-tissue fullness in the right cavernous sinus that extended posteriorly to the Meckel cave with enlargement of the right superior ophthalmic vein and mild proptosis. This supported the clinical diagnosis of a posttraumatic CCF. A cerebral angiogram delineated not only the expected direct CCF, but also a PPTA (Figs. 1A and 1B).

Neuroradiologic intervention with balloon occlusion of the PPTA resulted in occlusion of the direct CCF with preservation of flow in the right internal carotid artery (Figs. 2A and 2B).

Symptoms began to resolve by 10 days after intervention. One month after intervention, the abduction deficits and Horner syndrome remained, but after 3 months, the patient had no residual symptoms and minimal findings.

**DISCUSSION**

The primitive trigeminal artery develops at the 4-mm embryonic stage and disappears at the 7- to 12-mm stage. It is the most common of the carotid-basilar anastomoses to persist into adult life. In utero, the trigeminal artery supplies the basilar artery before the development of the posterior communicating arteries and the vertebral arteries. When these vessels develop, the trigeminal artery usually disappears.

The trigeminal artery arises from the proximal cavernous internal carotid artery with two distinct origins. If the artery runs lateral to the dorsum sella, its origin is from the posterolateral aspect of the cavernous internal carotid artery. If it has a midline course through or over the dorsum sella, the origin is from the posteromedial aspect of the cavernous internal carotid artery.
Two forms of PPTA exist: 1) fetal, in which the posterior circulation is dependent on the anastomosis; and 2) adult, where the posterior circulation is independent of the anastomosis. Our patient had the adult form of PPTA. The distal basilar artery opacified well on the vertebral injection (Figs. 2A and 2B), and the patient did not experience any adverse sequelae after occlusion of the PPTA. Presentation may be with acute subarachnoid hemorrhage, oculomotor pareses, trigeminal neuralgia, or internal carotid artery emboli transmitted to the basilar artery. Other entities that can be associated with a PPTA include aneurysm, arteriovenous malformation, and CCF (3,4,5).

The diagnosis of PPTA usually is made after an incidental finding. Before the introduction of magnetic resonance imaging techniques, PPTA could only be diagnosed with cerebral angiography. The presence of a PPTA does not affect blood flow direction if there is an associated fistula.

Therapeutic options of PPTA and CCF include balloon occlusion, direct surgical clipping, or prophylactic external-internal carotid bypass, in addition to proximal occlusion. Balloon occlusion is the preferred method of treatment; however, microcoils can be used if the lesion is not amenable to balloon occlusion. In our patient, balloon occlusion alleviated the symptoms. Before balloon occlusion, it must be determined that the fistula is not filling via the PPTA from the vertebral-basilar circulation; if the fistula fills via the vertebral-basilar circulation, the balloon must be repositioned. The risk of posterior circulation infarction is dependent on the direction of the flow in the PPTA and the size of the native basilar artery; with a small native basilar artery, the risk of infarction is increased, whereas with a large native basilar artery, the risk of infarction is small.

Although PPTA is a rare radiologic finding, this case shows that a PPTA can be considered when one encounters the neuro-ophthalmologic findings of a CCF occurring despite trivial trauma.

REFERENCES
Chiasmal Compression Due to Obstructive Hydrocephalus

Marko D. Bogdanovic, MRCP, and Gordon T. Plant, FRCP

A 25-year-old man sought treatment for an 8-month history of blurred vision. It began in the nasal field OS and progressed to affect both eyes severely. Visual acuity was 6/60 OD and counting-fingers on the left. There was mild chronic disc swelling and pallor bilaterally (atrophy papilledema).

Visual field testing (Fig. 1A, B) indicated generally depressed visual fields with maximal loss in the lower temporal hemifields bilaterally. Central vision was lost on the left. Magnetic resonance imaging (MRI) showed ventriculomegaly caused by aqueduct stenosis (Fig. 2), congenital in origin. There is an associated Chiari malformation. The ballooning lamina terminalis of the third ventricle is displacing the optic chiasm anteroinferiorly (Fig. 3). The visual field loss is explained by a combination of chiasmal compression, bilateral optic nerve damage, and chronic papilledema. Cerebrospinal fluid (CSF) examination showed a normal protein content and cell count.

Third ventriculostomy was attempted but abandoned because the interventricular foramen could not be visualized, and an external ventricular drain was sited. A modest reduction in ventricular size occurred, but an Acinetobacter infection prevented any further attempt at ventriculostomy under image guidance. Once the infection had been treated, a ventriculo-peritoneal drain was inserted through a right parietal burr-hole. The left lateral ventricle and third ventricle remained markedly enlarged, however, and an additional ventriculo-peritoneal drain was required on the left. The ventricles were of normal size after this procedure, but unfortunately visual function did not improve. The papilledema resolved, and at follow-up optic atrophy was observed with no change in visual acuity or fields.

Enlargement of the third ventricle can cause many different field defects (1,2). These include unilateral and bilateral scotomata, binasal and bitemporal hemianopia, unilateral upper temporal quadrantanopia, homonymous hemianopia, and unilateral blindness. Maximal loss in the lower temporal quadrants might be expected because the relevant fibers lie posterosuperiorly in the chiasm, in the direct path of the enlarging ventricle. This field defect does not appear to be reported more commonly than the others, however.

FIG. 1. Goldmann perimetry of A: left and B: right eyes. The visual fields are generally depressed with maximal loss in the temporal hemifields bilaterally.
CHIASMAL COMPRESSION DUE TO OBSTRUCTIVE HYDROCEPHALUS

In some cases of hydrocephalus in adults, ventriculomegaly and neurologic dysfunction persist despite the presence of a functioning shunt. It has been suggested that in established cases there can be a loss in the elastic properties of the brain, which may prevent resolution of ventriculomegaly despite normalization of CSF pressure (3,4). It is hypothesized that ventricular enlargement is directly responsible for neurologic dysfunction. Increased CSF removal by adopting subatmospheric pressure levels in the shunt system has been reported to lead to resolution of ventriculomegaly and neurologic improvement. This persisted when standard pressure levels were reinstated and may reflect reversal of the changes in brain compliance (3,4). In our patient, irreversible neurologic damage is likely to have occurred to the visual pathways, because reduction of ventricular size to normal did not lead to clinical improvement. The need for a second shunt may have been related to the infection that occurred after the first procedure.

REFERENCES
Bilateral Orbital Pseudotumor With Suprasellar and Pulmonary Involvement: Report of a Case

Yu-Hung Lai, MD, Hwei-Zu Wang, MD, Rong-Kung Tsai, MD, William F. Hoyt, MD, and Bi-Fang Lee, MD

A 39-year-old man had bilateral proptosis and blurred vision for 1 week. Computed tomography and magnetic resonance imaging showed signs of bilateral orbital pseudotumor, a suprasellar mass, and pulmonary infiltration. Biopsies from retrolublar and bronchial sites showed similar inflammatory tissue. His disease resolved with pulsed corticosteroid therapy.

Key Words: Orbital pseudotumor—Systemic inflammatory pseudotumor.

The term orbital pseudotumor has been used to describe idiopathic orbital inflammation simulating orbital neoplasm (1–5). The condition is characterized by acute onset of exophthalmos, lid and conjunctival edema, decreased eye movement, and pain. It is more commonly unilaterally than bilaterally (1–6). Bilateral orbital pseudotumor has an increased incidence of systemic disease (2). We report a rare case of bilateral orbital pseudotumor with cerebral and pulmonary involvement.

CASE REPORT

A 39-year-old man visited our outpatient department of ophthalmology with a 1-week history of progressive blurring of vision, pain, and proptosis OU. He had had flu-like symptoms several weeks earlier. His general health had been good except for 'sinusitis' operated on at a local hospital 2 months earlier. The family history was unremarkable.

His best corrected visual acuity was 20/200 OD and 20/25 OS. He had a 10-prism-diopter (10Δ) right esotropia. He had limited abduction, adduction, and depression OD and limited abduction OS (Fig. 1A). Hertel exophthalmometer readings were 21 mm OD and 20 mm OS.

An afferent pupillary defect was present OD. The conjunctivas were chemotic. Results of other ophthalmologic examinations such as intraocular pressure and fundus examination were normal.

Blood examinations were normal except for an elevated percentage of eosinophils (13%). Erythrocyte sedimentation rate was elevated (63 mm). Thyroglobulin antibody (78.2 IU/ml; normal range, < 25 IU/ml) and microsomal antibody (90 IU/ml; normal range, <25 IU/ml) were mildly elevated. Results of thyroid function tests indicated hypothyroidsm (thyroid-stimulating hormone [TSH], 2.4 μU/ml; normal range, 0.94–2.84 μU/ml; T3, 80.5 ng/dl; normal range, 98.4–144.2 ng/dl; T3U, 25.9%; normal range, 29.37–37.65%; T4, 2.9 μg/dl; normal range, 6.5–9.5 μg/dl; and free T3 index [FT3], 0.75; normal range, 2.19–3.13). Elevated EB-VCA (Epstein-Barr-viral capsid antigen) immunoglobulin G (IgG) (1:160; significant if > 1:40) and positive HLA-DR were detected. Results of tests for cytoplasmic pattern of antineutrophil cytoplasmic antibody (c-ANCA), antinuclear antibodies (ANA), rheumatoid factor, Venereal Disease Research Laboratory (VDRL) test, EB-VCA IgM, blood sugar, blood urea nitrogen (BUN), creatinine, electrolytes, and routine analysis of urine were normal. The angiotensin-converting enzyme level was not measured because of unavailability of testing facilities.

Visual-evoked responses (VER) showed poor responses OU (worse OD) with increased latency and decreased amplitude to patterned reversal stimuli. Humphrey automated perimetry indicated visual field defect OU (worse OD). Roentgenograms of the skull were normal. A chest radiograph showed a mass around the carina and increased interstitial pattern in bilateral lower lung fields.

On computed tomographic (CT) scans of the orbit, there were poorly demarcated soft tissue masses in the lateral aspect of the right orbit along the lateral rectus muscle, in the apex of the right orbit, and in the superolateral aspect of the left orbit (Fig. 2A). Right ethmoid sinusitis and bilateral maxillary opacities also were noted. In addition, an irregular, well-enhanced soft tissue mass was found in the suprasellar region, near the right parahippocampal gyrus and the cavernous sinuses bilaterally (Fig. 3A). Magnetic resonance imaging (MRI)
FIG. 1. A: Bilateral proptosis and limited abduction (OD) were noted before the corticosteroid treatment. B: Only residual limitation on abduction of his right eye was noted after the treatment.

showed similar findings (Fig. 3B). CT scan of the chest showed interstitial thickening in both lungs, a mildly enhanced soft tissue mass in the middle and lower third of the esophagus, and enlarged lymph nodes at pretracheal and prevascular areas (Fig. 4).

Bronchoscopy showed, in addition to a bulging mass around the carina, multiple segments of the bronchi with hyperemia and concentric narrowing. Biopsy of lesions in the trachea and bronchi showed chronic nonspecific round-cell inflammation. No malignant cells were found in the specimens (Fig. 5A, B). In pathologic examinations of all the specimens from the excisional biopsy of the retrobulbar tissue (1 x 0.5 x 0.2 cm³), there were no noncaseating granulomatous nodules or giant cells, which are characteristic of sarcoidosis. The specimens only showed chronic inflammation compatible with a diagnosis of orbital pseudotumor. No malignant cells or signs of vasculitis could be found (Fig. 5C, D). Results of a nasopharyngeal examination were normal. Gallium-67 scan indicated an increased activity in lacrimal glands, paranasal sinuses, and lung fields bilaterally.

The patient received 500 mg methylprednisolone intravenously twice per day for 3 days, and then he received 60 mg prednisolone orally once per day on successive days.

Three weeks after onset of his disease, visual acuity was 20/20 OU, he had 15-prism diopter (15Δ) of esotropia. There was no residual limitation of eye movement except abduction OD (Fig. 1B), and there was no afferent pupillary defect. Hertel exophthalmometer readings were (OD 13 mm; OS 14.5 mm), and Humphrey automated perimetry was normal OU.

Prednisolone was gradually tapered over the next 5 months. CT scans showed residual enhancing soft tissue masses in the superolateral aspect of each orbit (Fig. 2B). No mass could be found in the chest or intracranially. He has been maintained on low doses of oral prednisolone and azathioprine.

FIG. 2. CT scan of the orbit. A: Before the corticosteroid treatment, axial views showed inflammatory soft tissue masses in the lateral aspect of the right orbit along the lateral rectus muscle and its tendon, in the apex of the right orbit, and in the superolateral aspect of the left orbit. B: Residual well-enhanced soft tissue masses were noted in the superolateral aspect of the bilateral orbits after the treatment.
DISCUSSION

Orbital inflammation may result from Graves orbitopathy, sarcoidosis, vasculitis, lymphoma, Kimura disease, or orbital pseudotumor (1,2,7). Although our patient had hypothyroidism, the clinical features (acute onset; ocular pain; elevated erythrocyte sedimentation rate [ESR]; and infiltrative mass with extraocular muscle enlargement, including tendinous insertion) were not typical of Graves orbitopathy. In addition, his dramatic response to corticosteroid therapy also made Graves orbitopathy unlikely. The hypothyroidism may have been related to the inflamatory involvement of his pituitary gland or stalk.

Although angiotensin-converting enzyme test is not available in our hospital, there was no sign (clinical or laboratory) of sarcoidosis involving lung, skin, eyes, nervous system, heart, kidneys, or the musculoskeletal system. Serum angiotensin-converting enzyme (ACE) levels were increased in approximately 63.5% of the biopsy-proven sarcoid (8). Pathologically, there were no characteristic findings of sarcoidosis in a biopsy specimen from the orbit (as large as $1 \times 0.5 \times 0.2 \text{ cm}^3$ in size), which makes a diagnosis of sarcoidosis unlikely.

A diagnosis of vasculitis such as Wegener granulomatosis is not likely, for the following reasons: First, no signs of Wegener granulomatosis were found in the respiratory tract, kidneys, musculoskeletal system, eye, and skin. Second, there was no pathologic evidence of necrotizing granulomatous vasculitis in the tissue samples from lungs or orbit. Moreover, there was no support for this diagnosis from laboratory studies: the negative c-ANCA, negative rheumatoid factor, normal urinalysis, and normal blood studies.

Kimura disease or angiolymphoid hyperplasia with eosinophilia preferentially affect skin of the head and neck (7). In lids and orbits, the lesions are usually single. Multiple subcutaneous nodules, sometimes associated with eosinophilia (of peripheral blood), have been reported, particularly in Asians. Although there was eosinophilia of the peripheral blood of our patient, no other signs supported a diagnosis of Kimura disease.

Because of the dramatic response to the steroid therapy, the lack of malignant cells in biopsy tissue, and the lack of other evidence of lymphoma, a diagnosis of lymphoma was improbable. Biopsy of orbital lesions and lung lesions indicated a similar process of chronic inflammation compatible with the diagnosis of inflammatory pseudotumor.
Orbital pseudotumors are usually unilateral (1-6). Bilateral orbital pseudotumor in adults usually suggests a systemic disorder, as was true in our patient. The pathologic findings in orbital pseudotumors vary, without obvious differences between unilateral and bilateral cases (5).

Orbital pseudotumor with systemic involvement has been reported as a manifestation of multifocal fibrosclerosis. This is a disease of unknown cause, characterized by fibrous lesions occurring at a variety of sites such as mediastinum, retroperitoneal loci, thyroid, bile ducts, and orbits (3,9). The histologic diagnosis of multifocal fibrosclerosis depends on finding extensive deposition of hyalinized fibrous tissue, commonly arranged in more or less concentric whorls around extinct or attenuated blood vessels. A diagnosis of multifocal fibrosclerosis is not likely in our patient.

There have been cases with solitary nonorbital inflammatory pseudotumors (3) involving lungs (10,11), brain (12), gallbladder (13), and esophagus (14). Histologically, nonorbital pseudotumors are composed of fibrous tissue with an inflammatory cell infiltrate. Unlike in their orbital counterparts, the dominant cell population consists of spindle or plasma cells (3,10-14). To our knowledge, these pseudotumors do not occur in association with orbital pseudotumors.

Only a few cases of orbital pseudotumor have been reported with intracranial extension (15,16) or nasal sinus involvement (17). The case presented here had bilateral orbital pseudotumor with pulmonary and intracranial involvement. After systemic corticosteroid therapy, the lesions in lungs and brain disappeared, along with the shrinkage of the orbital pseudotumor. This therapeutic response provides evidence that the inflammatory processes in the orbit, lungs, and brain were identical.

REFERENCES


Ophthalmic Artery Microembolism in Giant Cell Arteritis

Barbara Schäuble, MD, Christine A.C. Wijman, MD, Behrooz Koleini, MD, and Viken L. Babikian, MD

A 70-year-old man presented with a history of headache and sudden loss of vision of the left eye. Funduscopic examination showed sector retinal edema and hemorrhage as well as optic disc swelling consistent with anterior ischemic optic neuropathy. The Westergren sedimentation rate was 66 mm/h. Temporal artery biopsy was consistent with giant cell arteritis. Routine transcranial Doppler testing performed on a Pioneer 2020 instrument (Nicolet Vascular, Inc., Golden, CO) equipped with special software for microembolus detection showed a microembolic signal in the left ophthalmic artery. During a subsequent monitoring study, microembolic signals were detected in the anterior and middle cerebral arteries, bilaterally. Microembolism can occur in giant cell arteritis. Ophthalmic artery microembolism can be detected in vivo by transcranial Doppler ultrasonography. This new imaging capability can potentially be useful when evaluating patients with vascular disorders of the eye.

Key words: Ophthalmic artery embolism—Retinal ischemia.

Giant cell arteritis (GCA) is a generalized, necrotizing arteritis characterized by inflammation of the cranial branches of the aortic arch as well as the coronary arteries. Ophthalmologic and neurologic manifestations occur in more than 30% of patients. Although retinal ischemic events are considered the result of inflammatory obstruction of vessels with or without distal embolism (1), the exact mechanism of ischemia in this context is not well understood. The "gold standard" to diagnose GCA is histopathologic confirmation of the clinical impression. Supportive evidence can be obtained by contrast angiography and color duplex imaging. These modalities rarely provide information regarding the mechanism of disease. In patients with atherosclerotic cerebrovascular disease, microembolic signals (MES) detected by transcranial Doppler ultrasonography correspond to platelet-fibrinogen microemboli (2). MES are predictors of current retinal and hemispheric ischemic events and are associated with symptoms of retinal ischemia (3). The presence of MES in patients with GCA has not been studied. In this report, we present transcranial Doppler findings in a man with biopsy-proven GCA.

CASE REPORT

A 70-year-old man had a 3-day history of sudden loss of vision OS. He volunteered a 1-week history of jaw pain when chewing, bifrontal headaches, and fatigue. He denied muscle aches and weight loss. The medical history and general examination were nonrevealing. There were no cardiac murmurs. Examination of the forehead showed a firm and tender left temporal artery. Ophthalmologic examination showed a best visual acuity of 20/30 OD and counting fingers at 3 feet OS. A left afferent pupillary defect was present. A sector of retinal edema and hemorrhage was seen temporal to the optic disc OS, and was suspicious for an occluded cilioretinal artery. In addition, diffuse swelling of the left optic disc was consistent with anterior ischemic optic neuropathy. GCA was suspected clinically, and intravenous methylprednisolone was administered.

Westergren sedimentation rate was 66 mm/h, and the hemogram was normal. A duplex study showed less than 30% stenosis of the extracranial carotid arteries. The patient refused echocardiographic studies. Results of the electrocardiogram were normal. Biopsy of the left temporal artery confirmed the diagnosis of GCA (Fig. 1). Transcranial Doppler examination 5 days after presentation on a Pioneer 2020 instrument (Nicolet Vascular Inc., Golden, CO) showed no evidence of internal carotid artery siphon stenosis. A MES was detected in the left ophthalmic artery (Fig. 2) during the regular examination. Subsequent MES monitoring studies indicated multiple MES in the middle and anterior cerebral arteries, bilaterally.

During a 10-month follow-up period, the visual acuity of the OS remained the same, and there were no retinal, hemispheric, or systemic ischemic events. The dose of prednisone was tapered, and the Westergren sedimentation rate normalized.
DISCUSSION

Our findings show that microembolism can occur in GCA. Whether it contributes to ocular or cerebral ischemic symptoms in this disease remains unknown.

Although MES can be detected in approximately 5% to 10% of controls without symptoms of retinal or brain ischemia, their frequency is low and their arterial distribution is limited in that setting. The finding of multiple MES in both anterior and middle cerebral arteries and the left ophthalmic artery of our patient suggests the presence of an active source of emboli, possibly located in the aortic arch or cardiac chambers. The coronary arteries and aortic arch can be affected by the arteritic process in GCA. However, the source of microemboli could not be determined.

Retinal emboli are often detected clinically, but the true prevalence of retinal embolism remains unknown for lack of a technology that permits to reliably detect these particles. Our observation suggests that it is possible to detect ophthalmic artery microemboli with transcranial Doppler. However, several technical limitations, including the development of a device to immobilize the probe over the orbit, need to be resolved. In addition, the issue of safety needs to be addressed. This is a critical limitation because prolonged exposure to ultrasound can cause cataract formation. Although insonation of the ophthalmic artery and internal carotid artery siphon at...
reduced ultrasound power is now considered an integral part of routine transcranial Doppler testing, the safety of prolonged exposure associated with MES monitoring is not established. Further research should help clarify this point.

Acknowledgement: The authors thank Dr. Flaviu Romanul for reviewing the biopsy slides and Val Pochay for his technical assistance in preparing the graphic material.

REFERENCES

Synkinetic Blepharoclonus

Daniel E. Jacome, MD

Objectives: To analyze the clinical data and test results collected in a group of patients exhibiting eyelid-closure blepharoclonus (BLC) on clinical neurologic examination.

Materials and Methods: Thirty-five patients were referred for neurologic evaluation for reasons other than BLC. Clinical electrophysiologic evaluations, including cranial nerve testing and electromyograms, were done according to standards. All patients had neuroimaging studies, including brain magnetic resonance imaging and head computerized tomography, or both, and many had electroencephalograms. Additional tests were done based on the patient's symptoms or reasons for referral.

Results: Eight patients had reflex BLC. Two cases were precipitated by vertical gaze; one of these patients had hereditary palmoplantar keratoderma and cataractry, and the other patient had Ehlers-Danlos syndrome and familial BLC. Other precipitants included speech in four cases, postural changes in two cases, and light stimulation in one case. Two patients had generalized myoclonus independent of their BLC, two patients had a history of sleep myoclonus, and several patients had BLC-associated facial myoclonus. One patient had BLC-associated myoclonus of the right shoulder. Synkinetic cranial movements were detected in 11 patients (four oculofacial, three oculolingual, one oculolingual, two dual cases, and one case of imitation synkinesis.) Three patients had familial BLC, seven patients had congenital developmental disorders, six patients had synkinetic tremors, and six patients had restless feet. Some indication of peripheral neuropathy was evident in eight patients.

Conclusions: Eyelid-closure BLC is an underrecognized, sporadic or familial, mostly benign, chronic eyelid-movement disorder that may be associated with tremors, myoclonus, cranial synkinesis, and restless feet. Reflex mechanisms may be identified in some patients. Gaze-induced BLC seems to have the greatest clinical relevance. In the current series, there were no examples of posttraumatic BLC, multiple sclerosis, hydrocephalus, or blepharospasm conditions previously reported to be associated with BLC. No electroencephalographic abnormalities were recorded during BLC, ruling out eyelid-closure epilepsy.

Key Words: Blepharoclonus—Blepharospasm—Cranial synkinesis—Eyelids—Movement disorder—Myoclonus—Synkinetic movements.

Blepharoclonus is the repetitive, easily detectable, myoclonic contractions of the orbicularis oculi muscle (1). It is commonly apparent with light eyelid closure and may be suppressed by forceful eyelid contraction (2). In contradistinction, blepharospasm (BLS) is a focal dystonia manifested by forceful and sustained involuntary closure of the eyelids, often accompanied by great difficulty in opening the eyes on command or free will, which is a clinical phenomenon called "apraxia of lid opening" (3,4). However, attempts to open the eyelids during episodes of BLS may be confused with BLC, or with paretic tremors of the eyelids in a patient with partial denervation of the orbicularis oculi. Blepharoclonus may be provoked by stretching of the orbicularis oculi or by gaze deviations (5,6). Synkinetic BLC is defined here as:

1. the involuntary movements, fasciculations, or facial electromyogram (EMG) motor units firing, triggered by, or associated with BLC, normally affecting muscles other than the orbicularis oculi;
2. BLC-enhanced cephalic and extracephalic focal, multifocal, or generalized tremors;
3. BLC in patients exhibiting other cranial synkinesis (synkinetic movements);
4. reflex BLC.

The last subgroup may be identified by the specific mechanism that causes BLC (see below). Those mechanisms are stretching of the orbicularis oculi, stimulation by sudden illumination, speech, changes in body posture, and gaze deviations. Although both patients reported by Obeso et al. (5) had reflex BLS and BLC, either one of these conditions may occur independently. In reflex BLS, the eyes are involuntarily forcefully shut, while in pure-reflex BLC, only rapid myoclonus of the eyelids is observed in the absence of sustained contraction of the orbicularis oculi.

MATERIALS AND METHODS

After a few patients with BLC referred for other neurologic disorders were identified by the author, a systematic search for this condition was performed for all new patients in the author’s practice. A total of 35 patients with BLC, ranging in age from 11 to 75 years, was collected over a 5-year period. These patients were identified on routine neurologic examination when asked to...
### Table 1. Reflex synkinetic blepharoclonus

<table>
<thead>
<tr>
<th>Patient/Sex/Age (y)</th>
<th>Signs</th>
<th>Diagnoses</th>
<th>Symptoms</th>
<th>Tests</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/38</td>
<td>Action tremors of hands, frequent nonstel foot movements at rest; BLC with light eyelid closure enhanced by sitting or standing, greatly diminished lying down</td>
<td>Demyelinating multifocal optic neuritis and peripheral neuropathy of unknown etiology; synkinetic (reflex) BLC</td>
<td>Objects blurred, lacked color in vision OS; V/A 20/20</td>
<td>VERS showed conduction slowing through optic nerve OS, brain MRI: normal; EMG legs: complex polyphasic MUPs recorded over leg muscles; no spontaneous activity</td>
<td>Progressive improvement of vision in follow-up with no new symptoms</td>
</tr>
<tr>
<td>2/F/43</td>
<td>Hypermobile joints, soft skin with very visible veins, tenderness of the spine, left leg weakness, abnormal gait; downward gaze BLC and myokymia of lower eyelid; speech-related BLC: akinesia of teeth</td>
<td>Synkinetic BLC; common migraine; EDS-related LS plexopathy; subcortical nodular gliosis</td>
<td>Back pain, numbness, tingling of left leg; left side pelvic heads without waking, sensitive teeth</td>
<td>LS spine MRI: normal; brain MRI: T2-weighted axial subcortical white matter; high-intensity signals of greater prominence over the left frontal region; EMG of legs: spontaneous normal MUPs at rest over both TA and left EDB muscles</td>
<td>Family history of EDS, spondylitis, ophthalmic eyelid closure BLC</td>
</tr>
<tr>
<td>3/F/44</td>
<td>BLC with upward gaze; palmar-planter hyperkeratosis, greasy over feet (Fig. 1)</td>
<td>Palmarplantar keratoderma, focal leukodendroplasia, cataracty, sciatric, gaze-evoked BLC</td>
<td>Sudden falls precipitated by emotions, without loss of consciousness; right leg postexertional pain</td>
<td>EEG, EOG, MRI of the LS spine; 2D echocardiogram; normal, no organomegaly by CT of the abdomen; EMG of the right leg; right sciatic, MRI of the brain; demyelination (Fig. 2), Haxxen-Brummer A, Hylslipidemia A, plasma amino acid levels, cellular cholesterol esterification normal Brain MRI/MRA, CNT, CT, MRI of LS spine, VERS BAERs: normal</td>
<td>Family history of hemophilia, common migraine</td>
</tr>
<tr>
<td>4/F/44</td>
<td>Chronic ptosis and miosis OD; action tremors of hands on flexion-extension at the wrists; frequent involuntary movements of feet at rest; eyelid-closure BLC; bilateral involuntary myoclonic contractions of the orbiculosis eyes with lateral gaze; frequent blinking (40-50 blinks/min); BLC triggered by unique light stimulation without LOC</td>
<td>Cluster headaches with residual chronic ipsilateral Horner syndrome; synkinetic BLC</td>
<td>Episodic severe pain behind right eye, numbness of right thigh and right side of face</td>
<td>Brain MRI: normal; negative MUPs present •</td>
<td>Negative</td>
</tr>
<tr>
<td>5/F/47</td>
<td>Eyelid-closure BLC triggered by speech and light stimulation</td>
<td>Migraine with aura, synkinetic BLC</td>
<td>Pounding headaches preceded by compulsive yawning</td>
<td>Brain MRI: normal</td>
<td>Father had migraines preceded by compulsive yawning</td>
</tr>
<tr>
<td>6/F/50</td>
<td>BLC with right eyelid closure, greatly enhanced in supine position</td>
<td>Synkinetic BLC, drug reaction: limited continuous facial muscle fiber activity</td>
<td>Diplopia and transient confusion after ingestion of lorazepam</td>
<td>Brain MRI: normal; CNT: normal MUPs present at rest over right orbiculosis oris and both mentalis muscles on facial EMG; Anti-Yo, Anti-Ri antibodies: negative</td>
<td>Breast cancer by history; no previous history of Bell palsy</td>
</tr>
<tr>
<td>7/F/66</td>
<td>BLC with eyelid closure and during speech; palmar deviation of jaw with lateral gaze; generalized deep-tendon hyporeflexia</td>
<td>Monoclonal gammopathy-associated peripheral neuropathy, synkinetic BLC, cerebrospinal synkinesis, specifi induced BLC</td>
<td>Intermittent numbness of limbs and left side of face</td>
<td>IgG lambda monoclonal gammopathy; C-spine MRI: normal; C-spine MRI: complex prolonged polyphasic MUPs over RF and EDB muscles with no F-waves responses; negative</td>
<td>Hypertension</td>
</tr>
<tr>
<td>8/F/73</td>
<td>Eyelid closure and speech-induced BLC; tends toward left when sitting; rigidity, akinesia of right arm</td>
<td>Synkinetic BLC, corticobulbar gageonic degeneration, truncal dystonia</td>
<td>Writing tremors, poor mobility, abnormal posture</td>
<td>Head CT: cortical atrophy; EOG, CNT, SPECT: normal</td>
<td>Negative</td>
</tr>
</tbody>
</table>

- BAER: brain stem auditory-evoked response; BLC: blepharoclonus; CNT: cranial nerve testing; CT: computed tomography; EDB: extensor digitorum brevis; EOG: electro-oculography; Ig: immunoglobulin; LOC: loss of consciousness; LS: lumbosacral; MRA: magnetic resonance angiogram; MRI: magnetic resonance imaging; MUP: motor unit potentials; RF: rectus femoris; SPECT, single photon emission CT; TA: tibialis anterior; V/A: visual acuity; VSR: visual-evoked response.
lightly close their eyelids for a minimum of 10 seconds. The
patients were also examined for clinical or electrophysiologic cranial nerve testing evidence of facial synkinesis and for evidence for any reflex precipitants, includ-}

<table>
<thead>
<tr>
<th>Patient/SEX/</th>
<th>Signs</th>
<th>Diagnoses</th>
<th>Symptoms</th>
<th>Tests</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>F/14</td>
<td>Synkinetic BLC with bilateral facio-oculo-torticollis</td>
<td>Generalized morning headache, photophobia, phonophobia</td>
<td>Normal EEG, EMG/NCV of the brain</td>
<td>Mother and sister had somnambulism</td>
<td></td>
</tr>
<tr>
<td>F/17</td>
<td>Synkinetic BLC; action tremors of the hands on flexion-extension of wrists; restless feet; hypermobile joints; scoliosis; fusion of second and third toes on each foot; unilateral twitching of muscles and cutaneous reflexes with ipsilateral gaze</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F/20</td>
<td>Synkinetic BLC; action tremors of hands on flexion-extension of wrists; restless feet; hypermobile joints; scoliosis; fusion of second and third toes on each foot; unilateral twitching of muscles and cutaneous reflexes with ipsilateral gaze</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F/23</td>
<td>Synkinetic BLC; action tremors of hands on flexion-extension of wrists; restless feet; hypermobile joints; scoliosis; fusion of second and third toes on each foot; unilateral twitching of muscles and cutaneous reflexes with ipsilateral gaze</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F/25</td>
<td>Synkinetic BLC; action tremors of hands on flexion-extension of wrists; restless feet; hypermobile joints; scoliosis; fusion of second and third toes on each foot; unilateral twitching of muscles and cutaneous reflexes with ipsilateral gaze</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F/27</td>
<td>Synkinetic BLC; action tremors of hands on flexion-extension of wrists; restless feet; hypermobile joints; scoliosis; fusion of second and third toes on each foot; unilateral twitching of muscles and cutaneous reflexes with ipsilateral gaze</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

See Table 1 for definitions of additional abbreviations.
CSF, cerebrospinal fluid; NCV, nerve conduction velocities; TPO, thyroid peroxidase antibody.
reflex mechanism (Table 1), associated tremors (Table 2), myoclonus (Table 3), synkinesis movements (Table 4), or presence of synkinesis evident by facial EMG only (Table 5). The patients were examined by the author on more than one occasion and followed for a minimum of 2 years. There was no consanguinity among the patients examined. The patients were referred for neurologic consultation for reasons other than BLC. The majority of patients were women, in part due to local patterns of referral that include gynecologists in the role of primary care physicians.

Patients either did not experience or were not incapacitated by their eye twitching, but most were aware of their involuntary eyelid movements, especially at night when they closed their eyes before falling asleep. None were aware of having cranial synkinesis. Myoclonus was distinguished from tremors based on the larger amplitude and slower frequencies of the movements in myoclonus. Restless feet consisted mostly of rotational movements of the feet while sitting or lying down and was differentiated from restless legs by the lack of sensory symptoms or premonitory urge to move the legs, the absence of premonitory urge to move the feet, and the lack of sensory symptoms while sitting or lying down and was differentiated from restless legs by the lack of sensory symptoms.

RESULT#s

Of the eight patients with reflex BLC, none exhibited BLS or had BLC provoked by stretching of the orbicularis oculi muscle. Blepharospasm was not observed in the three patients with frequent blinking rates (>30/min). Gaze-evoked BLC was present in two patients; one patient had Ehlers-Danlos syndrome and familial BLC, and the other patient had hereditary palmoplantar keratoderma, focal hemispheric subcortical demyelination (lekkoencephalopathy), and cataplexy without narcolepsy.

### TABLE 3. Blepharoclonus and myoclonus

<table>
<thead>
<tr>
<th>Patient/Id</th>
<th>Symptoms</th>
<th>Signs</th>
<th>Diagnosis</th>
<th>Tests</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>17/F25</td>
<td>Daily global headaches, burning sensation between scapulas</td>
<td>Neuralgia paresthesia; chronic daily headaches; synkinetic BLC</td>
<td>EMG/NCV of left leg, CNT, brain MRI: normal; EEG: normal background with focal spikes and waves, generalized, non-specific theta discharges without clinical manifestations</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>18/F79</td>
<td>Muscle pain, postobstructive exertion, global daily headaches</td>
<td>Synkinetic BLC, action tremors of hands, restless feet; axonal peripheral neuropathy</td>
<td>EMG, brain MRI: normal; EEG of legs: complex prolonged MUPs; no neurologic manifestations</td>
<td>Hashimoto thyroiditis by history; IBS; chronic daily headaches; anxiety disorder; fibromyalgia</td>
<td></td>
</tr>
<tr>
<td>19/F70</td>
<td>Severe, constant right temple pain</td>
<td>Synkinetic BLC; temporal arteritis (?)</td>
<td>Brain MRI, CSF studies: normal; temporal artery biopsy negative; sedimentation rate: 42 mL/hr; TPO titer: 160 ml, euthyroid</td>
<td>Hashimoto thyroiditis, IBS</td>
<td></td>
</tr>
<tr>
<td>20/F75</td>
<td>Sterile (noninfectious) myoclonus, synkinetic myoclonus</td>
<td>Myoclonus, stereotypic &quot;rubbing&quot; pain; generalized severe body twitching triggered by startle</td>
<td>Brain MRI, head CT, EEG: normal; delayed right R2 component of blink reflex</td>
<td>Remote history of twitching spasm of left side of face relieved by posterior fossa vascular decompression: hypertension</td>
<td></td>
</tr>
<tr>
<td>21/F74</td>
<td>Dizziness, poor balance, headaches with visual aura aborted by repetitive voluntary eye movements; episodes of abrupt-onset generalized sweating</td>
<td>Synkinetic BLC, paroxysmal hyperhidrosis</td>
<td>Normal head CT</td>
<td>Ulcerative colitis, osteoarthritis, migraine with aura, family history of migraine</td>
<td></td>
</tr>
</tbody>
</table>

See tables 1 and 2 for definitions of additional abbreviations.

IBS, irritable bowel syndrome.

TABLE 4. Blepharoclonus and synkinectic movements

<table>
<thead>
<tr>
<th>Patient/Sex/ Age (y)</th>
<th>Signs</th>
<th>Diagnosis</th>
<th>Symptoms</th>
<th>Tests</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>22/M/12</td>
<td>Eyelid-closure BLC; ipsilateral deviation of jaw with lateral gaze (Figs. 3A, B, and C)</td>
<td>Mental temporal sclerosis, secondary generalized seizures, eyelid-closure BLC, oculopterygoid synkinesia</td>
<td>Recent onset of tonic-clonic seizures</td>
<td>Normal EEG; brain MRI, CT; right temporal ventricular enlargement and right mental temporal atrophy with no enhancing lesions</td>
<td>Congenital (surgically corrected) encephalocele and imperforated anus; family history of polydactyly</td>
</tr>
<tr>
<td>23/F/14</td>
<td>Light eyelid-closure BLC with alternating periods of rapid slow myoclonic eyelid contractions; ipsilateral elevation of eyebrow and jaw deviation with lateral gaze</td>
<td>BLC with oculopterygoid and oculofrontalis synkinesias; facial BLC, episodic tension headaches</td>
<td>Pressure-like bilateral headaches</td>
<td>CNT, head CT: normal</td>
<td>Asthma</td>
</tr>
<tr>
<td>24/M/20</td>
<td>Rhythmic elevation of eyebrows with eyelid-closure BLC; postural and action tremors of hands; tendency of neck on palpation; hypnagogic deep tendon reflexes</td>
<td>Synkinectic BLC, posttraumatic headaches, cervical spine; congenital Arnold Chiari malformation and cervical syrinx</td>
<td>Headaches and neck pain after lateral whiplash injury</td>
<td>Normal EEG; Arnold Chiari malformation detected on brain MRI; small central syrinx on cervical MRI</td>
<td>Negative</td>
</tr>
<tr>
<td>25/F/22</td>
<td>Elevated optic discs with no exudation or peripapillary hemorrhages; normal venous pulsations; eyelid-closure BLC; ipsilateral jaw deviation with lateral gaze; obesity</td>
<td>Idiopathy intracranial hypertension? (declined lumbar puncture); “icepick-like” pain; synkinectic BLC, oculopterygoid synkinesis</td>
<td>Headaches, sharp head pain; blurred vision 30 times/4 (“like looking through glass”); dizziness, occasional tinnitus</td>
<td>Normal EEG, brain MRI, head CT; CNT; MUPs at rest recorded from frontalis, orbicularis oris, and mentalis muscles bilaterally, greater on left side</td>
<td>Family history of epilepsy; congenital strabismus corrected with surgery during childhood</td>
</tr>
<tr>
<td>26/F/25</td>
<td>BLC, action tremors of hands, ipsilateral deviation of jaw with lateral gaze, occipital multifocal muscle fasciculations of limbs</td>
<td>Posttraumatic basilar artery migraine, facial motor axonopathy and (restricted) continuous muscle fiber activity; synkinectic BLC; oculopterygoid synkinesis</td>
<td>Recurrent occipital headaches, neck pain, blurred vision after minor head trauma</td>
<td>EEG, brain MRI, NCV of left arm: normal; CNT; abnormal polyphasic MUPs recorded over right mentalis and orbicularis oris muscles; MUPs at rest of left mentalis and both frontalis muscles</td>
<td>Negative</td>
</tr>
<tr>
<td>27/M/31</td>
<td>BLC with right eyelid closure; bilateral contracture of chin muscles on lateral gaze</td>
<td>Synkinectic BLC, postinfectious etiologic tube dysfunction, anxiety disorder, episodic tension headaches</td>
<td>Global pressure headaches; occasional cracking sound of right ear after acute sinusitis</td>
<td>Brain MRI, CNT, EMG-NCV of left arm: normal</td>
<td>Negative</td>
</tr>
<tr>
<td>28/F/34</td>
<td>Alternating “see-saw” elevation of eyebrows during speech; light eyelid-closure BLC; forceful opening of mouth induced yawning (Fig. 4); no echoepraesthesia otherwise</td>
<td>Focal epilepsy: complex partial seizures with secondary generalization; “icepick-like” pain; synkinectic BLC, limbus BLC, oculopterygoid synkinesis</td>
<td>Episodes of confusion and automatic behavior preceded by bad taste in mouth, exceptionally terminating in convulsions</td>
<td>Brain MRI, CT; normal; EEG: generalized slow wave discharges; CNT: absent right R1 blink reflex component; abnormal polyphasic MUPs of bilateral frontalis muscles</td>
<td>Negative</td>
</tr>
<tr>
<td>29/F/35</td>
<td>Monocular BLC, action tremors of hands, restless feet, toxic pupils, focal nodular atrophy of subcortical disease; extreme startle response to unexpected stimulus; ipsilateral deviation of jaw and tongue with lateral gaze</td>
<td>Synkinectic and monocular BLC, oculopterygoid and oculofrontalis synkinesias; hyperexcitability, continuous muscle fiber activity syndrome, restless feet, hypokinesia, continuous muscle fiber activity, hypokinesia, continuous muscle fiber activity</td>
<td>Headaches, back pain, nocturnal leg muscle twitching, postexertional exhaustion</td>
<td>CNT, MRI of L5-splint, EEG, left quadriceps muscle nerve biopsy and NCV of legs: normal; negative PMP-20 genetic deletion or duplication; EMG of legs: spontaneous MUPs at rest of gastrocnemius, TA, and EDB muscles</td>
<td>Posttraumatic stress disorder; bipolar affective illness; asthma</td>
</tr>
<tr>
<td>30/F/40</td>
<td>Right facial weakness and contracture; pulling of right corner of mouth with blink; eyelid-closures BLC</td>
<td>Synkinectic BLC; otoneural left retiroarcolar pain, postparalytic facial synkinesias, facial contracture</td>
<td>Pain behind left ear with mensae; chronic pulling sensation of right side of face; muscle twitching after ipsilateral Bell palsy years earlier; facial twitching worse with mesae</td>
<td>Brain MRI, EEG, CSF studies; normal; CNT: toxic motor unit discharges recorded over right pyramidalis major muscle with eye closure; BLC: complex prolonged MUPs over right facial muscles (chronic reinnervation); no denervation</td>
<td>Negative</td>
</tr>
</tbody>
</table>
Blepharoclonus was induced by speech in only two patients. In addition, one patient with light-induced BLC and one patient with gaze-induced BLC also exhibited speech-induced BLC. Speech-induced BLC was distinguished from BLC-like tics during normal speech on the basis of a longer duration and a larger amplitude of eyelid myoclonus in the former. In addition, these patients had eyelid-closure BLC. Unconscious sustained closure of the eyelids during speech may have precipitated the appearance of BLC in these four patients. Specific posture was the precipitating mechanism of BLC in two of the patients. Several patients had BLC-associated facial myoclonus, but there were two patients with generalized myoclonus independent of BLC and two patients with nocturnal (sleep) myoclonus. One patient had BLC-induced focal myoclonus of the right shoulder. Seven patients had BLC-associated tremors, three patients had abnormalities detected by facial EMG only, and 11 patients had BLC-synkinetic movements (three oculofacial and three oculopterygoid cases, and one oculolingual case; Figs. 3A–C). There were two cases of dual synkinetic movements; one with oculolingual and oculopterygoid synkinesis, and the other with oculofacial and oculopterygoid synkinesis. One patient had imitation synkinesis (reflex yawning with imitation of yawning by widely opening her mouth; Fig. 4), and another patient was unable to close her right eye voluntarily. One patient exhibited monocular BLC in isolation, and another patient had asymmetric BLC. One patient had alternating rapid and slow BLC. Three patients with familial BLC and seven patients with congenital developmental disorders are described. Restless legs syndrome was present in six patients, three of whom had features of peripheral neuropathy. Eight patients had signs or symptoms of mild axonal peripheral neuropathy, including examples of continuous muscle fiber activity syndrome. Three patients had Hashimoto thyroiditis, but they were euthyroid and had low thyroid peroxidase antibody titers. There were no examples of multiple sclerosis or brain tumors. One patient had a cerebellar venous angioma (Fig. 5).

### TABLE 4 (Continued)

<table>
<thead>
<tr>
<th>Patient/Sex/ Age (y)</th>
<th>Signs</th>
<th>Diagnosis</th>
<th>Symptoms</th>
<th>Tests</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>31/F/36</td>
<td>Eye-closure BLC; mild contraction of corners of mouth with eye blinks; sustained, eyelid-closure induced upward pulling of right corner of mouth; unable to wink OD</td>
<td>Recurrent vestibular neurotisis; synkinesis BLC</td>
<td>Paroxysmal nonpositional vertigo</td>
<td>CNT: normal MUPs present at rest; over both central muscles; brain MRI, EEG, CSF studies, and EMG/NCV of left arm; normal</td>
<td>No history of Bell palsy; no evidence of subclinical peripheral neuropathy</td>
</tr>
<tr>
<td>32/F/56</td>
<td>Eyelid-closure BLC; ipsilateral deviation of the tongue with lateral gaze</td>
<td>Vestibular neurotisis, congenital venous angioma, eyelid-closure BLC, oculolingual synkinesis</td>
<td>Dizziness</td>
<td>EEG: nonspecific brief generalized theta episodes while awake; brain MRI; right cerebellar venous angioma (Fig. 5); normal CNT</td>
<td>Nocturnal myoclonus and hypertension</td>
</tr>
</tbody>
</table>

See Tables 1 and 2 for definitions of additional abbreviations. PMP, peripheral myelin protein.

### TABLE 5. Blepharoclonus and EMG synkinesis

<table>
<thead>
<tr>
<th>Patient/Sex/ Age (y)</th>
<th>Signs</th>
<th>Diagnosis</th>
<th>Symptoms</th>
<th>Tests</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>33/F/15</td>
<td>Rapid blinking (&gt;30/min); eyelid closure BLC</td>
<td>Familial synkinesis BLC</td>
<td>Pounding, recurrent bilateral headaches</td>
<td>Brain MRI and EEG: normal; CNT: MUP discharges both mental and right orbicularis oris muscles with right lateral gaze</td>
<td>Asthma, seasonal depression, migraine without aura; mother and maternal grandmother had similar BLC</td>
</tr>
<tr>
<td>34/M/42</td>
<td>Pain on pressure applied behind right ear, radiating to ipsilateral frontal region and eye; mild right facial hemiatrophy (no history of facial palsy)</td>
<td>Congenital facial hemiatrophy, synkinesis BLC, ontocentosis of C-spine, grey auricular neuralgia, sleep myoclonus</td>
<td>Intermittent right retroauricular pain, generalized nocturnal body twitching</td>
<td>Brain MRI with contrast and EEG: normal; sleep myoclonus recorded during overnight sleep studies; C-spine x-rays; D2/D; CNT: MUPs at rest recorded at right mentalis muscle during right eyelid closure</td>
<td>Negative</td>
</tr>
<tr>
<td>35/F/75</td>
<td>Frequent blinking (&gt;50/min); eyelid-closure BLC, hypoxia in left ear</td>
<td>Midbrain lacunar stroke? synkinesis BLC</td>
<td>Transient diplopia with downward gaze</td>
<td>Head CT: normal; CNT: spontaneous normal MUPs of orbicularis oris bilaterally at rest and during eyelid closure</td>
<td>Osteoarthritis</td>
</tr>
</tbody>
</table>

See Tables 1 and 2 for definitions of additional abbreviations. DJD, degenerative joint disease.
Two patients had epilepsy but exhibited no focal epileptic activity related to eye movements or eyelid closure during their electroencephalograms (EEGs). Details of the clinical data and results of testing for each patient are listed in the accompanying tables, which divide the different subgroups.

DISCUSSION

I believe BLC is underdetected because it is not spontaneously reported by patients; its presence is frequently missed by the examiner during routine neurologic examination because the patient is asked to close his or her eyes only briefly, not waiting long enough for BLC to appear after a variable latency period, or because he or she is asked to close the eyes forcefully (to determine the presence of facial weakness), while at the same time suppressing BLC.

Previously recognized causes of BLC are head trauma, hydrocephalus, and multiple sclerosis (1,2,6,7). Multiple sclerosis was the underlying condition in the two patients of Keane (6) with gaze-evoked BLC. Obeso et al. (5) reported the case of a patient with essential BLS. None of the patients herein reported experienced major head trauma, had evidence of hydrocephalus, had signs of multiple sclerosis, or had BLS. Three patients had Hashimoto thyroiditis (patients 13, 18, and 19), but they were euthyroid and had no cognitive disturbance or alteration of consciousness level. Their blood thyroid peroxidase titters were not significantly elevated to explain their BLC on the basis of Hashimoto encephalopathy that potentially may have caused myoclonus of the orbicularis oculi muscles (8). History of Bell palsy was elicitable only in two patients (patients 19 and 30), and only two patients (patients 32 and 34) had nocturnal (sleep) myoclonus. No patients showed evidence of epilepsy on EEG during BLC, including the two individuals with epilepsy, and no patients exhibited EEG epileptic activity associated with their tremors, synkinesis, or myoclonus. Although six patients (patients 1, 4, 9, 10, 18, and 29) had restless feet, and three patients (patients 4, 33, and 35) had frequent blinking, none developed additional involuntary movements, including dystonia, BLS, and oculogyric crisis.

Patient 3 had palmoplantar keratoderma, which is an inherited condition recently reported in association with leukoencephalopathy (9) (Fig. 1). She presented with painful gaze-evoked BLC and cataplexy similar to the cases of Niemann Pick disease type C (10). Her brain MRI showed a small globular area of hyperintensity on the T2-weighted images localized to the left centrum semiovale, which was consistent with focal demyelination (Fig. 2). However, her cultured skin fibroblasts did not demonstrate the cytochemical abnormalities typical of Niemann Pick disease type C (10). To my knowledge, neither of these clinical signs have been reported in patients with palmpoplantar keratoderma.

Cranial synkinesis is often overlooked by the examiner because it is rarely symptomatic. Some signs are very subtle and require close examination because synkinetic facial movements may be isolated, unsustained, or of small amplitude; they may be congenital or acquired, as in the example of synkinesis after Bell palsy, in which case they are more apparent. Many types have been described before and after the landmark paper on the subject by Schwarz (11) in 1962. The pathogenesis of synkinetic BLC cannot be ascertained. In cases with no apparent immediate cause, aberrant crossed innervation established during fetal development of the cranial nerves may be postulated. Patient 34, who had congenital facial hemiatrophy, is an example that supports the de-
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Fig. 3. A–C: Lateral jaw deviation with lateral gaze (oculopterygoid synkinesis) (patient 22).

Developmental theory. In acquired cases (i.e., after Bell palsy), misdirected regeneration of cranial nerve axons is the usual explanation without excluding the potential participation of the mechanisms of peripheral ephapsis and central synaptic reorganization (11–13). Because synkinetic movements do not always involve the facial muscles, it cannot be proposed in every case that the associated movements were precipitated by peripheral facial nerve fibers, or that BLC represents an abnormality of the innervation of the obicularis oculi muscle. In examples of BLC-induced or enhanced tremors, a state of central hyperexcitability could be added, although future additional electrophysiologic testing with somatosensory-evoked potentials and transcranial magnetic stimulation are needed on similar patients in order to support this hypothesis.

The original reports on BLC suggest that its presence constitutes a sign of major neurologic illness (1,2). None of these patients suffered from a serious progressive neurologic illness, at least on a short-term basis. Instead, the clinical data presented here indicate the following:

1. BLC is a focal tremor of the obicularis oculi, at times forming part of more widespread benign tremors or myoclonus;
2. BLC can be the expression of a familial trait (as in patients 10, 23, and 33);
3. BLC often constitutes an isolated fortuitously discovered clinical sign;
4. BLC at times is associated with (underdiagnosed) cranial synkinesis and has a benign course in most individuals;
5. BLC may have different precipitants, but gaze-evoked BLC probably has the greater clinical relevance or is more likely to be found in individuals with active or progressive neurologic disease (i.e., multiple sclerosis, Niemann Pick disease, palmoplantar keratoderma).

REFERENCES


Functional Magnetic Resonance Imaging of Lateral Geniculate Nucleus at 1.5 Tesla

Atsushi Miki, MD, PhD, Jonathan Raz, PhD, John C. Haselgrove, PhD, Theo G. M. van Erp, MA, Chia-Shang J. Liu, BA, and Grant T. Liu, MD

Although activation of the lateral geniculate nucleus has been detected by functional magnetic resonance imaging with magnetic field strengths higher than 2.0 Tesla, there have been no reports of functional magnetic resonance imaging of the lateral geniculate nucleus with the more widely available 1.5 Tesla scanner. The authors used functional magnetic resonance imaging techniques at 1.5 Tesla to detect lateral geniculate nucleus activation in five of seven healthy subjects. This study shows that visual activation of the lateral geniculate nucleus can be obtained with functional magnetic resonance imaging using conventional 1.5 Tesla scanners.

Key Words: Functional magnetic resonance imaging—Lateral geniculate nucleus—Visual cortex—1.5 Tesla.

The lateral geniculate nucleus (LGN), a deep subcortical structure of the thalamus, is the location of the first synapse in the afferent visual pathway. Most of the fibers from retinal ganglion cells terminate there, and postsynaptic neurons of the LGN project to the primary visual cortex.

Although there are many reports of activation of visual cortex using functional magnetic resonance imaging (fMRI) techniques (1,2), there have been only a few reports of fMRI of the LGN. Although the signal increase was small relative to that of the visual cortex, LGN activation has been found by fMRI using magnets at 2.0 Tesla (T) or higher (3-7). However, these MRI systems are not widely accessible, and most are experimental. To our knowledge, there have been no reports of LGN activation detection using fMRI with the more widely available 1.5T MRI scanners. We investigated whether it was possible to detect activation of the LGN by fMRI with a conventional 1.5T MR scanner.

METHODS

Seven healthy volunteers (four men and three women; mean age, 23.7 years; range, 22–27) gave informed consent before participating in this study. The consent form was approved by the Institutional Review Board of the Children's Hospital of Philadelphia. All subjects had normal visual acuity, confrontational visual fields, and stereopsis. All subjects were examined twice and underwent the second session 2 to 7 days (mean, 4.5) later.

Imaging was performed with a clinical 1.5-T MRI system (Vision; Siemens, Erlangen, Germany). The subjects' heads were padded with foam padding within the quadrature head coil to restrict motion. Subjects were instructed to hold their heads still. Sixteen oblique axial images that were positioned parallel to the calcarine fissure were collected for anatomic images using a T1-weighted spin echo sequence. Thereafter, 16 functional images were acquired on the identical and parallel slices of the anatomic images using a T2*-weighted echo-planar image sequence (time to recovery/time to echo = 1.68/64 ms [3 second interscan interval]; flip angle = 90°; matrix = 64 × 64; field of view = 240 mm; in-plane resolution = 3.75 × 3.75 mm²) with the slice thickness of 5 mm without interslice gap. One hundred twenty image sets of 16 images were acquired for functional imaging. Light-proof binocular goggles with 6 × 5 light-emitting diodes (modified S10VSB; Grass Instruments, Quincy, MA) flashing at the frequency of 8 Hz were placed over subjects' eyes to provide binocular full-field visual stimulation. The subjects were instructed to keep their eyes open during the visual stimulation. The visual stimuli were turned on and off with the use of a trigger from the magnet. Ten scans of visual stimulation of both
TABLE 1. Location of lateral geniculate nucleus (LGN) activation in Talairach coordinates

<table>
<thead>
<tr>
<th>Subject</th>
<th>Location (X, Y, Z)</th>
<th>Z-score</th>
<th>Location (X, Y, Z)</th>
<th>Z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-22, -30, 5</td>
<td>4.74</td>
<td>26, -26, 0</td>
<td>6.27</td>
</tr>
<tr>
<td>2</td>
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<td>4.50</td>
<td>22, -26, 5</td>
<td>5.39</td>
</tr>
<tr>
<td>3*</td>
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<td>5.83</td>
<td>26, -26, 5</td>
<td>5.39</td>
</tr>
<tr>
<td>3†</td>
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<td>6.78</td>
<td>22, -26, 0</td>
<td>7.01</td>
</tr>
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<td>5*</td>
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<td>5.38</td>
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<td>5.27</td>
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<tr>
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<td>-26, -26, 5</td>
<td>6.01</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* first study; † second study.

eyes (epochs 1, 3, 5, 7, 9, and 11) alternated with ten scans of darkness (epochs 2, 4, 6, 8, 10, and 12).

DATA ANALYSIS

Data analysis was performed on UNIX workstations with IDL (Interactive Data Language) and SPM96 (Wellcome Department of Cognitive Neurology, London, UK) packages. The first five scans of echo-planar images were discarded to eliminate magnetic saturation effects. The average signal intensity of each image in the functional image set was normalized to compensate for baseline drift of the magnetic resonance signal. Functional images of each subject were realigned using a six-parameter (three translations and three rotations) rigid body transformation to the first volume. After this, the images were transformed into the anatomic space of Talairach and Tournoux (8). This spatial normalization routine was performed by minimizing the sum of squares difference between the functional images and the echo-planar images template, using an 8-parameter affine transformation. Data were smoothed with a Gaussian filter (full width at half maximum = 8.0 x 8.0 x 10.0 mm). A box-car delayed by 6 seconds and temporal smoothing were used. T-statistics were calculated for each voxel in an 8-parameter affine transformation. Data were smoothed with a Gaussian filter (full width at half maximum = 8.0 x 8.0 x 10.0 mm). A box-car delayed by 6 seconds and temporal smoothing were used. T-statistics were calculated for each voxel and then transformed into z-values (SPM [Z]). In all subjects, Z > 4.5 approximately corresponded with P < 0.05 after the correction for multiple comparisons in the entire image.

RESULTS

Statistically significant (P < 0.05 after the correction for multiple comparisons) activation was observed in the bilateral LGN in five subjects (Table 1), in addition to the activation of the visual cortex in all subjects. Two subjects showed bilateral LGN activation in both studies, and the activated areas in the LGN were consistent across the studies, separated by several days (Figs. 1 and 2). The other two subjects showed bilateral LGN activation in only one study. Another subject had bilateral LGN activation in one study and unilateral LGN activation in the other study.

DISCUSSION

The position of LGN activation was consistent with the known anatomic locations (9) and also with the previous fMRI reports at higher magnetic field strengths (3–7). Also, the three-dimensional location of LGN ac-
activation in the standard space was almost constant for all subjects.

Activation of LGN has been identified using flash goggles (6), checkerboard (3,5,7), and a visual motion task (4). Although the optimal visual stimulus for detecting this nucleus using fMRI remains to be investigated, our study shows functional mapping of LGN can be performed by fMRI at 1.5T, even with standard flash goggles.

The activation of LGN could not be found in two subjects and was not reproducible in some subjects. This is probably because of our relatively large voxel size, the use of spatial filter in our study, and the relatively small size of the LGN (partial volume effects) (10). In addition, visual activation using fMRI can vary substantially within and between subjects, in part because of changes in head position, the subjects’ attention to the stimulus and level of arousal, or the state of the MR scanner (e.g., temperature) (11).

We have shown that functional mapping of the LGN can be performed with a conventional, widely available 1.5T MR scanner. Although the LGN has been imaged using anatomic MR images (9), fMRI may provide an adjunctive localization method of this small nucleus in living human subjects. This should allow more neuroophthalmologists and other clinical investigators the opportunity to study the LGN in healthy subjects and in subjects with visual deficits, for example, by permitting precise clinico-pathologic comparisons. Future investigations with fMRI at 1.5T may also include a detailed retinotopic mapping of the LGN and a study of patients with retrogeniculate lesions and retrograde degeneration.

REFERENCES
Idiopathic Horner Syndrome in the Golden Retriever

Pip Boydell, B Vet Med, MRCVS

Objectives: Various reports have noted a high incidence of idiopathic Horner syndrome in golden retriever dogs. The author seeks to document this condition in the breed.

Materials and Methods: A prospective study was made of cases of Horner syndrome in dogs referred to the author throughout a 10-year period. As part of the general clinical, ophthalmic, and neurologic examination, denervation hypersensitivity testing was performed to localize the responsible lesion. Follow-up results were obtained in all cases by repeat examination or telephone contact.

Results: Of 155 dogs in the study, 110 were golden retrievers, 100 of which were diagnosed as having idiopathic second order Horner syndrome. Ninety-five of the golden retrievers were male, some neutered. Signs resolved spontaneously in all cases within 6 months.

Conclusions: There is a high incidence of idiopathic second order Horner syndrome in the male golden retriever.

Key Words: Horner’s syndrome—canine—denervation hypersensitivity.

Horner syndrome results from interference with the sympathetic innervation of the eye and adnexa. Clinical signs in dogs (Fig. 1) include anisocoria; incomplete dilation of the affected pupil in low-light conditions; enophthalmos; and third eyelid protrusion, ptosis, and an increase in temperature of the face and pinna resulting from peripheral vasodilation.

The sympathetic pathway to the eye can be divided schematically into three parts: central, preganglionic, and postganglionic (1). The site of the responsible lesion can be determined by denervation hypersensitivity testing (2; Boydell P. The accuracy of denervation hypersensitivity testing with 10% phenylephrine eyedrops in Horner’s syndrome in the dog, Presented at the Proceedings of the 30th Annual Meeting of the American College of Veterinary Ophthalmologists, Chicago, 1999). Ten-percent phenylephrine drops instilled into the conjunctival sac will lead to mydriasis after an amount of time dependent on the position of the lesion in the sympathetic pathway. When the postganglionic neuron is affected, mydriasis will occur within 20 minutes. In cases with a preganglionic lesion, mydriasis is expected 20 to 45 minutes after administration. Previous reviews have shown that the cause remains undiagnosed in approximately half the affected dogs, and trauma accounts for a large proportion of those cases that are diagnosed (3-5). Reported etiologies in the dog include congenital anomalies, central nervous system infection, neoplasia, ischemic myelopathy and intervertebral disc disease, brachial plexus avulsion, carotid artery catheterization and surgery of the carotid body, thoracic and cervical neoplasia, thoracic drain placement, surgery of the shoulder joint, middle ear disease and its management, trigeminal neuritis and orbital disease, and cervical spinal disease (6-15). Idiopathic Horner syndrome has been described in the golden retriever (16), but no reference has been made to the relative incidence.

METHODS

A prospective study was made of cases of dogs with Horner syndrome referred to the author throughout a 10-year period (1987–1997) at several different centers. Breed, age, and sex were recorded, and all patients underwent a complete general clinical, ophthalmic, and neurologic examination. These examinations included routine hematology and blood biochemistry screens (albumen, globulin, urea, creatinine, liver enzymes, cholesterol, bile acids, and electrolytes); thyroid function testing; and chest, neck, and head radiographs. Computed tomography was performed in only one instance as part of an orbital work-up. Other investigations, such as endoscopy of the tympanic bullae and electrosurgical investigation, were performed when appropriate. Dogs referred for the investigation of other clinical signs, and in which Horner syndrome was also noted, were included in this study, but those dogs that only presented with Horner signs and an underlying cause for the signs were determined were included in the study. Denervation hypersensitivity testing was performed, instilling one drop of 10% phenylephrine eyedrops (Martindale Pharmaceuticals, Romford, UK) and timing the appearance of substantial pupillary dilation. One drop was placed in the ventral conjunctival sac OU, and the eyes were assessed at 5-minute intervals. No other pharmacologic tests were performed.
RESULTS

One hundred fifty-five dogs presenting only with signs of Horner syndrome were investigated. Ocular examination was unremarkable except for the Horner signs. There was a relevant history of trauma to the head, neck, or axilla in 12 dogs. Blood tests were performed in 108 dogs and results were unremarkable in all instances, except for 2 dogs in which there was evidence of hypothyroidism.

Radiographic examination of the chest and neck was performed in 58 dogs. Anterior thoracic neoplasia (lymphoma and mediastinal adenocarcinoma) was detected in 2 cases, and evidence of otitis media was evident in 14 dogs. Signs of middle ear disease were detected by otoscopy in 22 dogs (including the 14 dogs in which there were radiographic signs). Orbital ultrasonography and computed tomography demonstrated a soft tissue mass in one dog. Electromyography showed involvement of the brachial plexus in three cases.

Of the 155 dogs in the sample, 110 were golden retrievers or golden retriever/Labrador retriever crosses. In 100 of these golden retrievers, no cause for the Horner signs was apparent. Sixty-one dogs were unneutered males, 34 dogs were neutered males, and 5 dogs were neutered females. Of the 45 dogs of other breeds, no cause for the Horner signs was identified in 10 cases.

In all the idiopathic cases, the time recorded for dilation of the Horner pupil after instillation of 10% phenylephrine drops was 35 to 45 minutes. The contralateral control pupil dilated after 60 to 90 minutes. The age range of the retrievers with idiopathic Horner syndrome was 2 to 10 years, with an average age of 5.28 years. In all these cases, the third eyelid protrusion and ptosis resolved within 30 minutes, noticeably before substantial pupillary change.

Two dogs were reported to have impaired visual function; this symptom was attributed to excessive protrusion of the third eyelid. No treatment was given, and all idiopathic cases had partial or complete resolution of Horner signs within 16 weeks of the initial examination. All idiopathic cases had resolved completely within 6 months of the initial examination. No recurrence has been reported in any of these patients.

Exact numbers of the hospital population of referred golden retrievers and all breeds are not available because the studies involved several different centers. However, numbers are available for the past 3.5 years when the number of dogs referred to the Animal Medical Centre in Manchester was 8,876. Two hundred sixty-nine of these dogs were golden retrievers, and 7 of these had idiopathic second order Horner syndrome. Three idiopathic second order cases were noted in other breeds during this time at this clinic. The incidence in golden retrievers was 2.6%; the incidence in all other breeds was 0.03%, and the incidence in all breeds was 0.11%. Chi square analysis gives a 0.01 to 0.02% chance that this difference in incidence could occur by chance alone.

DISCUSSION

No accurate numbers of breed populations in the United Kingdom are available, although golden retriever numbers are high in the Kennel Club registration. Similarly, there are no available data concerning the sex of pet dogs in the general population. Thus, there is no possible statistical correlation between the breed incidence of Horner syndrome in dogs seen at a single referral center and the breed incidence of Horner syndrome in dogs in the general population. However, the results of this study suggest that golden retrievers have a relatively high incidence of idiopathic Horner syndrome, and male dogs are much more likely to be affected. Although full details of the relative populations are not available, it is unlikely that there would have been substantial changes during the past 10 years, and some interpretation may be made of the relative incidence in the data acquired from a single center for 42 months.

Disease involving the middle ear was seen to be the second most common cause of Horner syndrome in the dog. The accuracy of pharmacologic localization of the site of a lesion in the sympathetic pathway has been questioned, and emphasis has been placed on the importance of accompanying clinical signs (3,4). The author has found the technique of denervation hypersensitivity testing using 10% phenylephrine drops to be easy to perform, consistent, and reliable in cases in which a cause has been determined, although Kay (2) comments that the test can be subjective and inconsistent. When no other localizing signs are available, this test assumes greater importance. Pharmacologic localization of the responsible lesion in Horner syndrome has been documented using other agents, such as hydroxyamphetamine and cocaine in dogs and people (17-19), but these agents

FIG. 1. Golden retriever with idiopathic Horner syndrome.
were unavailable in the United Kingdom during this study. However, it is unlikely that the use of these agents would have added any additional information because the results of the tests using phenylephrine were considered definitive. Epinephrine has been used, but this agent is thought to be of minimal use because of reported poor corneal penetration and a wide variation in sensitivity (17,20).

By definition, the etiology remains undetermined. Many patients were boisterous and were reported to pull on the lead, often with a choke chain, and it can be surmised that this may lead to minor traumatic damage to structures within the neck, including the sympathetic pathway. Arguments against this position are that one might expect to see a greater incidence in puppies and immature dogs during training. Similarly, there are other breeds that have a reputation for pulling against restraint, yet have no apparent predisposition toward the condition. Although there is no evidence of a hereditary nature, the high breed incidence suggests some inherited component or predisposing feature. The author can offer no explanation for the predominance of male dogs affected, although male dogs, perhaps, had a tendency to pull harder against normal restraint of collar and lead or choke chain. Such a theory remains speculative, but no others have been offered. However, anecdotally, veterinary ophthalmologists and neurologists recognize the high incidence of idiopathic Horner syndrome in the breed. The author welcomes any explanations.

REFERENCES

Letters to the Editor

To the Editor:

The authors thank Kaminski et al. for commenting on our paper (1). They raise an important concern—did this patient actually have myasthenia gravis (MG)? We too initially had a concern over the diagnosis. The initial findings did not include ptosis but only a subtle, fleeting gaze incompatibility and atypical accommodative findings. The abnormal accommodative findings were similar to those previously reported in another paper in which traditional tests confirmed the diagnosis of MG (2). The consulting neurologist thought that it would be prudent to obtain a visual evoked potential (VEP) to rule out demyelinating disease, even at this late stage. Our patient refused a Tensilon (Zeneca Pharmaceuticals, Wilmington, DE), and single-fiber electromyogram (EMG). In this era of informed consent and the Internet, the patient’s rights must be respected. Evaluation of circulating acetylcholine receptor antibodies, thyroid (T3, T4, thyroid-stimulating hormone [TSH]), and of the thymus were made (computed axial tomography [CAT] scan). Though not previously mentioned, because we considered these tests part of comprehensive neurologic examination to rule out MG, they were negative. In addition, we considered and ruled out chronic progressive external ophthalmoplegia, internuclear ophthalmoplegia, diabetes, intracranial lesions, and Lambert-Eaton syndrome (3,4).

The diagnosis of myasthenia was not made on the basis of the accommodative findings, but rather on the basis of the fatigability of the extracocular muscle system: ptosis, phoria, and fusional amplitudes—all of which showed measurements of progressive fatigue from morning to night over a period of months with a positive response to Mestinon (see Figs. 1 & 2) (1). The phoria and fusional amplitudes were accurately and objectively measured with cover test and prism bar while the examiner observed the position of the eyes. Tensilon and Mestinon are both anticholinesterases with similar response characteristics except duration. A successful clinical trial of Mestinon is virtually diagnostic of myasthenia gravis. Thus, a positive Tensilon (Mestinon) response to accommodation is strongly suggestive of a diagnosis of MG.

One of our intents was to make clinicians and researchers aware that specific and subtle abnormal accommodative findings (as well as vergence) may be the first sign of MG in the presbyopic population. Hence, measurements of accommodative facility might provide useful diagnostic information. Furthermore, a simple treatment such as appropriate spectacle correction to decrease both the accommodative and vergence demand may be very helpful in certain patients with MG. Finally, we hope that we might stimulate clinician(s) to evaluate accommodative facility in a larger sample of presbyopic MGs and determine how common these findings are.

Thank you for allowing us to address Kaminski et al.’s concerns.

Jeffrey Cooper, MS, OD
Gayle J. Pollak, OD
Kenneth J. Ciuffreda, OD, PhD
Philip Kruger, OD, PhD
Jerome Feldman, PhD
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New York, New York

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LETTERS TO THE EDITOR

To The Editor:

Cooper et al. (1), after reviewing the contradictory literature on the effects of myasthenia gravis (MG) on accommodation, presented a patient with accomodative insufficiency allegedly secondary to MG. Unfortunately, they did not establish that their patient had MG.

The patient had ptosis that did not fatigue and did not improve with the sleep test or ice test (a sensitive and very specific test for partial ptosis in MG [2]). The authors did not perform the other very basic, routine tests to improve with the sleep test or ice test (a sensitive and very specific test for partial ptosis in MG [2]). The authors did not perform the other very basic, routine tests to diagnose MG, such as Tensilon (Zeneca Pharmaceuticals, Wilmington, DE), which is safe in asthmatics pretreated with atropine, repetitive nerve stimulation, single-fiber electromyogram (EMG), or a determination of circulating acetylcholine receptor antibodies. Obtaining a visual evoked potential after the patient developed ptosis suggests neurologic naivety. The previous patient reported by these authors (3) did have a positive Tensilon test and a single-fiber EMG said to be confirmatory of MG.

The only diagnostic support they had for MG was “improvement” (although undocumented with photographs) of the ptosis with Mestinon (Zeneca). However, improvement with an anticholinesterase medication is not specific for MG but occurs in other neuromuscular conditions (4). Moreover, Mestinon affects muscarinic synapses in smooth muscle (5). Thus, alterations of accommodation after Mestinon do not establish a diagnosis of MG.

Michaelson et al. (6) reported antisarcinuclar acetylcholine receptor antibodies in MG, but there is no clinical or physiologic evidence to suggest that these are of pathogenic significance (7).

Although unrelated to the main point of the Cooper et al. report and our letter, the basis for the preferential involvement of the extraocular muscles in MG is more complex than stated (for review, see Kaminski and Ruff [8], and Kaminski [9]).

To the Editor:

We make the following brief points related to the Response by Cooper et al.:

1. Fatigability is only suggestive, but certainly not diagnostic, of myasthenia.

2. A clinical trial of Mestinon is not equivalent to a Tensilon test, nor did Sergott make that statement in his chapter (1). Thus, Daroff’s statement that a positive Tensilon test “is virtually diagnostic of myasthenia gravis” (2) is irrelevant in this context. Moreover, Daroff was referring to a positive Tensilon test properly interpreted, meaning resolution of eyelid ptosis, or the direct observation of the strengthening of an extraocular muscle, and not indirect measures, such as lessening of a phoria. The major point of Daroff’s paper was that a cover test, prism bar, red glass, Maddox rod, and other techniques, may give spurious responses to Tensilon testing, and direct observation is essential (2).

3. The authors did not establish the diagnosis of myasthenia gravis in their reported patient (3).

Henry J. Kaminski, MD
Robert B. Daroff, MD
Louis F. Dell’Osso, PhD
Cleveland, Ohio

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To the Editor:

Kim and Kosmorsky described a fascinating case that they called an arteriovenous malformation but incorrectly titled the paper Arteriovenous Communication in the Orbit.

I believe that the referring ophthalmologist made the correct diagnosis—that this case represented a dural cavernous fistula with retrograde orbital filling. The setting of symptoms after coronary artery bypass surgery is the perfect setting for dural fistulization. The proximal branches from the ophthalmicus, labeled “F,” appear to at least be in the anterior portion of the cavernous sinus. It
is not surprising that other muscular branches contributed to the fistula. The argument as to whether all dural fistulas represent arteriovenous malformation or are a result of the dynamic effect of partial venous thrombosis may remain controversial. The age of the patient suggests that this disease is acquired.

The most important films, showing selective right external carotid angiography that demonstrates the internal maxillary artery filling the superior ophthalmic vein and retrograde filling presumably of cavernous sinuses, appear to make this case a dural fistula of the most anterior aspect of the cavernous sinuses.

Norman J. Schatz, MD
Coral Gables, Florida

To the Editor,

Once again the keen eye of Dr. Schatz strikes at the heart of an issue. In our case report, we termed the lesion an arteriovenous malformation in a feeble attempt to gussy up the title of the paper. After reviewing the chart, we discovered that the lesion was termed an orbital dural-based fistula. The exact point of origin of this lesion cannot be determined precisely, but I would concede that an anterior cavernous sinus location is possible. Dr. Schatz also correctly notes that there is controversy in the terminology applied to these lesions; some pathologists would argue that a dural fistula is a type of arteriovenous malformation. Like Ivan Ivanovich, the great Russian wrestler, discovered, you can't win them all. Thank you, Dr. Schatz, for once again demonstrating that the oldest dogs can still do the neatest tricks.

Gregory S. Kosmorsky, DO
Cuyahoga Falls, Ohio

To the Editor:

I want to present a brief summary of a patient's case in hope that it might elicit information about similar cases from readers. A 50-year-old previously healthy woman developed binocular diplopia in her 20s. Further details are not available except that a cause could not be found, even after an extensive in-patient evaluation. She had several unsuccessful strabismus procedures. While in her early 40s, the diplopia worsened, and she began to have pain in her orbits precipitated by exertion or eye movements. She also complained that her eyes became red when she exerted herself. When this patient was evaluated for limb muscle pain precipitated by exertion, easy fatigue, and weakness, she was found to have McArdle disease. Her daughter, who has not been tested, has had some nonocular symptoms.

The patient's visual function is entirely normal, and she is emmetropic. Her upper lids look puffy, similar to the appearance of the lids in those with Graves ophthalmopathy. There is no lid retraction, ptosis, or lag. Exophthalmometry readings are 21 mm bilaterally, and the

Simmons Lessell, MD
Boston, Massachusetts

Caution During Performance of the Red-Green Glasses Test for Functional Visual Loss

To the Editor:

The red-green glasses test for detection of functional visual loss is performed by placement of the green filter in front of the eye with alleged visual loss and placement of the red filter in front of the eye with normal sight. Small red letters on a white sheet of paper are written lightly with a red pencil or a felt-tip pen. When performed correctly, the patient, who believes he or she is reading binocularly, will actually only be reading from the eye behind the green filter. Therefore, near vision in the eye with alleged visual loss may be objectively measured.

If the examiner presses too firmly when writing the red letters, however, an impression on the paper is created that may allow the patient to see the letters through either filter. The examiner should test (preferably not in the patient's view) whether the red letters are written sufficiently lightly so that they cannot be seen through the red filter. When performing this test, it is critical that the examiner place his or her own near correction, in addition to the red-green glasses. Although red letters through a red filter may not be apparent without correction, they may be visible when appropriate correction is placed. With my own near correction in place, I am surprised to see how lightly I must write with red pencil to prevent sight through the red filter.

The above proviso may avoid false-positive red-green glass test results and erroneous diagnoses of functional visual loss, especially in children.

Michael L. Slavin, MD
Long Island Jewish Medical Center
Albert Einstein College of Medicine
Great Neck, New York
To the Editor:

I read with interest the article by Sadda et al. (1) that describes the case of a patient with anomalous optic disc elevation. The authors found ultrasonographic evidence of increased subarachnoid fluid around the optic nerve, despite normal intracranial pressure results. Stimulated by similar findings in two patients, we have studied the meninges of the optic nerve in humans and have found a dense system of lymphatic capillaries in the dura of the optic nerve that probably represent a functional cerebrospinal fluid pressure regulating system. Labeling experiments indicate drainage of cerebrospinal fluid from the subarachnoid space of the optic nerve into the lymphatic capillaries in the dura.

Until now, the concept of a homogenous pressure in the entire cerebrospinal fluid compartment, including ventricles, subarachnoid space, and cysterns, has not been challenged. This concept, however, is based on hypothesis rather than on reliable measurements, which are notoriously difficult in compartments with small volumes.

Sadda et al. (1) carefully avoided the term papilledema in their paper. This may be justified according to current terminology because they did not find an elevated intracranial pressure in their patient. Based on the histologic findings described in our paper (2), and because the pressure in the different cerebrospinal fluid compartments may not necessarily be homogenous, I believe that their case might have been papilledema as a result of a local increase of the cerebrospinal fluid pressure that caused an optic nerve sheath tight compartment syndrome with elevated pressure in the subarachnoid space of the affected optic nerve.

H. Esriel Killer, PD Dr.med
Augenklinik, Kantonsspital Aarau, Switzerland

REFERENCES

Authors’ Reply

To the Editor:

Dr. Killer raises the question of whether the bilateral optic disc elevation in our patient (1), which we believe was congenital anomalous elevation, was actually localized papilledema, i.e., focal increased intracranial pressure related to abnormal regulation of cerebrospinal fluid drainage by the lymphatic drainage system in the meninges of the optic nerve, which Killer et al. (2) described in 1999. He postulates that this could account for the increased fluid detected by ultrasonography around the orbital portion of the optic nerves on three occasions in our patient, who never had evidence of increased intracranial pressure as tested by lumbar puncture.

We do not believe that this is the case, for several reasons. First, this patient’s optic disc elevation had been present for at least 20 years and was documented photographically over 10 years. If this were true disc swelling (localized papilledema), we would have expected some changes in the appearance of one or both nerves to occur over this period of time, particularly the development of optic disc pallor and peripapillary retinal nerve fiber layer defects, just as one would expect to see in a patient with untreated increased intracranial pressure or untreated focal compression of the optic nerve from an orbital mass. In addition, we would have expected the patient to have experienced some evidence of visual sensory dysfunction during this time. Therefore, although Dr. Killer’s speculations are intriguing, we do not believe they are correct. Of course, the best way to determine this would be to measure the cerebrospinal fluid pressure in the nerve sheath directly, as described by Liu and Michon (3) in 1995; however, these measurements were performed only in patients scheduled for enucleation or evisceration and would undoubtedly place our patient’s vision at some risk. Alternatively, we could measure visual evoked potentials in our patient; this might be a more sensitive indicator of compression of the nerve than our clinical assessment. In the meantime, we believe that it is most likely that the fluid that surrounds the optic nerves in our patient is the result of anomalous patulous optic nerve sheaths and does not represent trapped cerebrospinal fluid under pressure.

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