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Retinal Arteriovenous Malformation With Fluctuating Vision and Ischemic Central Retinal Vein Occlusion and Its Sequelae: 25-Year Follow-Up of a Case

Thomas G. Hardy, M.D., and Justin O'Day, M.D.

A patient with a retinal arteriovenous malformation (AVM) had experienced episodic visual loss with spontaneous recovery for many years, followed by permanent visual loss secondary to central retinal vein occlusion. She subsequently progressed to development of retinal neovascularization extending onto the posterior vitreous face with recurrent vitreous hemorrhage requiring vitrectomy. A brief review of the literature is presented, and the cause of the fluctuations in vision and central retinal vein occlusion are discussed.

Key Words: Central retinal vein occlusion—Retinal arteriovenous malformation—Retinal ischemia—Retinal neovascularization—Visual loss.

Abnormal arteriovenous communications of the retina, first described by Magnus in 1874 (1), are relatively rare findings and have been referred to by many different terms (2); the term retinal arteriovenous malformation (AVM) is used in this article.

Visual loss in association with retinal AVM may result from cystic degeneration of the retina (3,4), retinal exudation, retinal ischemia with neovascular glaucoma, traction retinal detachment (5), and, rarely, retinal hemorrhage (6). Other visual problems may arise from involvement of the optic nerve (7), chiasm (8), optic tract, and other central neural structures. However, these will not be discussed here. This report is of a patient with intermittent visual obscurations in whom a central retinal vein occlusion later developed with retinal neovascularization and vitreous hemorrhage, a complication that has not previously been reported.

CLINICAL RECORD

A 20-year-old female nurse in 1970 described a history of intermittent blurred vision in the right eye that was present at rest and occasionally worsened with exercise. The initial clinical findings were reported by Billson et al. (9) in the Australian Journal of Ophthalmology. Visual acuity at the time was 6/6 uncorrected in both eyes. Visual field examination showed small central and paracentral temporal scotomata on the right. A retinal AVM was found arising from the right optic disc and arching across the inferotemporal papillomacular bundle toward the macula. No other ocular abnormalities were found, and results of a general physical examination were normal. Fluorescein angiogram showed early and rapid flow through the AVM with several dilated capillaries and capillary loss between the loops of the AVM, but no leak was visible. There was no angiographic evidence of orbital or intracranial AVM.

The patient sought medical attention in July 1986 with a short history of episodic blurring of central vision in the right eye, fluctuating every 15 minutes from extremely dark to clearing; this resolved during the course of a day. Three days later, she again experienced considerable loss of vision, which subsequently improved over a few hours. This visual disturbance was worse at higher altitude while the patient was on a skiing holiday. Visual acuity was 6/9 in the right eye and 6/4 in the left.

FIG. 1. Fundus photograph showing the retinal arteriovenous malformation before development of central retinal vein occlusion (central retinal vein occlusion).
The left eye remained normal throughout the follow-up. Ophthalmodynamometry revealed systolic pressure of 60 mm Hg and diastolic pressure of 10 mm Hg in the right eye, with left eye pressures of 70 mm Hg systolic and 30 mm Hg diastolic. Funduscopic appearances were unchanged, apart from irregularity and slight dilation of the retinal veins (Fig. 1). A fluorescein angiogram again showed early filling of the AVM, and the capillary loss noted between the AVM loops had extended to the macula (Fig. 2).

The patient sought attention again in July 1993 with further episodic central visual obscurations and episodes of loss of the lower half of her right visual field. Later, persistent reduction of vision developed with visual acuity of 6/24. Intracocular pressure remained normal throughout the entire follow-up. A right central retinal vein occlusion was seen, with venous dilation and tortuosity and nerve fiber layer hemorrhages, perivascular sheathing of the AVM, and ischemic changes to the right papillomacular retina. Over the following week the patient described a further decline in vision, with visual acuity now 6/60. A right relative afferent pupil defect was present and persisted throughout. There was loss of color vision and the right paracentral scotoma persisted. A florid right central retinal vein occlusion was found, with a swollen optic disc and retinal pallor above the macula (Fig. 3). Another fluorescein angiogram showed early rapid filling of the AVM with capillary loss within the loops of the AVM also involving the macula (Fig. 4) and in the midvenous phase showed marked dye leakage from retinal veins and optic disc (Fig. 5). No hematologic abnormality was detected.

During the following months, there was a progressive decline in which vision was finally restricted to finger counting associated with progression of the central retinal vein occlusion and widespread retinal hemorrhages and ischemia (Fig. 6). In December 1993 there was substantial resolution of the retinal hemorrhages and sheathing of the AVM (Fig. 7). A fluorescein angiogram showed a poorly vascularized retina with reduced blood supply to the AVM.

In March 1994 peripheral retinal neovascularization was noted (Fig. 8), and 2 months later a vitreous hemorrhage was detected, requiring a course of panretinal photocoagulation. There was no development of rubeosis.
iridis. Recurrent vitreous hemorrhages over the next 7 months indicated the need for vitrectomy.

The final stable visual acuity in May 1996 was 6/18. The AVM had regressed dramatically (Fig. 9). A fluorescein angiogram revealed persistently delayed arm-retina time and macular hypoperfusion with a small amount of residual dye leak from the limbs of the AVM (Fig. 10).

**DISCUSSION**

Retinal arteriovenous malformation (AVM) is a well-recognized entity with approximately 90 cases described to date. The common finding is one or more abnormal communications between the arterial and venous retinal circulations, although the choroidal circulation has been involved in a minority of occasions (1,4,10,11). Cerebral AVMs may be associated with the retinal lesion (12,13) and the AVMs are congenital (14,15). Onset of symptoms usually occurs in the second to third decade (14-17) and includes visual impairment of varying degrees depending on the location of the AVM and any complications. Predominantly unilateral, there are rare bilateral occurrences (18). The natural history may be nonprogresive (15,16), progressive (2,5), or occasionally, self-resolving (6).

Archer et al. (2) classified retinal AVMs into three groups. Group 1 is characterized by an arteriolar or abnormal capillary plexus between the major communicating vessels that are usually localized to one sector of retina and are rarely progressive or decompensated. Group 2 AVMs, as exemplified in this case, have direct arteriovenous communications and appear to exhibit hyperdynamic flow through the AVM with resultant increased risk of exudation, hemorrhage, and thrombosis, although these complications are reportedly uncommon. Group 3 AVMs are most often associated with complications because of their large size and extent, displaying large-bore communicating channels vulnerable to hemodynamic stress and its sequelae. The frequency of association with cerebral AVM increases from group 1 to 3 (2,19,20).

The transient and fluctuating visual loss described in this case is a feature that has not been emphasized previously in reports of retinal AVM and is possibly secondary to a "steal" phenomenon, wherein the hyperdy-
neurinoma is ischemic. It is possible that the pre­

relative stasis and predisposition to thrombosis. The de­

...residual dye leak from arteriovenous malformation and macular hypoperfu­

FIG. 10. Fundus fluorescein angiogram showing residual dye leak from arteriovenous malformation and macular hypoperfu­

The dynamic nature of the flow through the AVM caused re­
duction in general retinal blood flow with episodes of ischemia and visual obscurations. Early in the course, the patient noted some exertional alteration in the visual loss that could support the notion of a steal occurring. The worsening with increased altitude would also support this hypothesis, subsequent to relative hypoxia. Several possible mechanisms to explain the retinal ischemia associated with retinal AVM have been described by Traboulsi (21) and Tomsak (22) and other investigators (5,23): ischemia resulting from chronic retinal steal and a critical reduction in retinal blood flow; partial throb­

...sion of the AVM with reduced blood flow to the retina supplied by the AVM, if indeed the AVM supplied some retinal tissue; or obstructed retinal venous outflow at the optic disc from the enlarged afferent or efferent vessels of the AVM. The second option is least likely in this case, given the good flow through the AVM seen on fluorescein angiogram. It is also possible that the ischemia was subsequent to venous hypertension, resulting from arterialization and obstruction downstream and therefore, local hemodynamic disturbance.

The permanent visual loss, however, may also be a result of the mechanisms mentioned earlier but is more likely to be consequent to the central retinal vein occlusion that had obvious implications for the macula but also caused widespread retinal ischemia. The most likely cause of the central retinal vein occlusion is compression at the disc by an enlarged venous limb or reduced blood flow secondary to steal by the AVM, with subsequent relative stasis and predisposition to thrombosis. The de­

...veloped of retinal neovascularization is not a common sequel to central retinal vein occlusion, even when the vein occlusion is ischemic. It is possible that the pre­

existing retinal ischemia resulting from the AVM contributed to new vessel formation in a manner similar to the iris neovascularization described by Bloom et al. (5) and Effron et al. (23). The subsequent events of vitreous hemorrhage and vitrectomy have not been previously described in the literature regarding retinal AVMs, although rubenoid glaucoma has been described.

This case is interesting in view of the fluctuating and then permanent retinal ischemia secondary to the AVM and the subsequent development of retinal neovascularization. The duration of follow-up is also significant, the longest previously documented follow-up had been 17 years (24).

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Retinal Ischemia in Aortic Arch Atheromatous Disease

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Retinal ischemia is often caused by emboli arising from the cardiac chambers or the common carotid artery bifurcation; the latter are often composed of cholesterol. However, in many patients no lesions are identified after evaluation of these sources of emboli. Two patients were observed who had retinal ischemia and emboli originating from aortic atheromatous plaques that were visualized by transesophageal echocardiography. Cardiac, carotid, and intracranial sources of emboli were excluded. The embolic nature of retinal ischemia was further corroborated by the presence of microembolic signals during transcranial Doppler insonation of the middle cerebral artery on the side ipsilateral to the symptomatic retina. In patients with Hollenhorst plaques the aortic arch can be a potential source of emboli. Transesophageal echocardiography should be considered in these patients when the initial evaluation does not identify a cardiac or carotid lesion.

Key Words: Aortic arch plaque—Retinal embolism—Retinal ischemia.

A common cause of transient monocular blindness and retinal artery occlusion is retinal embolism (1). Emboli may be composed of calcific material (2), fibrin and platelets (3), or, more commonly, cholesterol (Hollenhorst plaques) (2,4). The latter often arise from atheromatous plaques at the common carotid artery bifurcation (5). However, as many as 50% of asymptomatic patients with Hollenhorst plaques have no evidence of carotid disease (6), and in two thirds a source of emboli could not be found after carotid evaluation and precordial echocardiography (7). That the aortic arch can be the source of retinal ischemia is not well documented (8,9). We observed two patients with retinal ischemia originating from the aortic arch in whom the diagnosis was established by means of ultrasound and magnetic resonance imaging (MRI) tests.

CASE REPORTS

Case 1
A 91-year-old man suddenly lost vision in the lower half of his left visual field. He had no associated ophthalmologic or neurologic symptoms. Medical history included diet-controlled diabetes mellitus and coronary artery disease, for which he took aspirin. There was no history of headache, jaw claudication, neck or shoulder pain, previous transient visual loss, or cerebral ischemic events. On examination 2 days after onset of symptoms, visual acuity was 20/70 OD and 20/50 OS. There was an inferonasal quadrantic visual defect in the left eye. Retinal infarction in the distribution of the left superior retinal branch artery secondary to an embolus was noted (Fig. 1A). General, cardiac, and neurologic examinations were unrevealing.

Erythrocyte sedimentation rate was 31 mm/hr. A carotid duplex study showed minimal plaque formation at the origins of both internal carotid arteries, causing diameter reductions estimated at less than 30%. Brain MRI showed an old lacunar infarct in the left caudate nucleus. A magnetic resonance angiogram showed normal intracranial arteries and left common and internal carotid arteries. A plaque causing 50% to 70% luminal diameter reduction was detected in the right common carotid artery. A transthoracic echocardiogram (TTE) showed hypokinesis of the left ventricle but no embolic source. A transesophageal echocardiogram (TEE) showed calcified plaques in the aortic arch and the ascending and descending aorta (Fig. 1B). The largest in the arch was 8 mm thick. No mobile elements were seen. Diffuse left ventricular hypokinesis was again observed, and no intracardiac thrombus was found. A transcranial Doppler ultrasound (TCD) study performed 7 days after onset of symptoms showed more than 60 microembolic signals in the left middle cerebral artery during a 30-minute recording (Fig. 1C). No signals were detected on the right side. Microembolic signals persisted in the left middle cerebral artery and were again absent on the right during a repeat TCD study 6 days later. The laboratory's TCD methods have been described in a previous report (10).

A diagnosis of retinal embolism and infarction was
made. The suspected source of emboli was an aortic arch plaque distal to the right and proximal to the left common carotid artery ostia.

Case 2
A 67-year-old man had a history of two attacks of transient loss of vision of the right eye. He described both as though a shade were being pulled over the eye. The attacks were 24 hours apart. The first lasted 3 hours and the second lasted 30 minutes. There were no other accompanying neurologic or cardiovascular symptoms. His medical history included hypertension, hyperlipidemia, chronic renal insufficiency, and diabetes mellitus. Approximately 1 year previously, he had had transient symptoms of vertebrobasilar ischemia for which he was prescribed warfarin. International normalized ratio was 3.0 at the time of present symptoms. Physical examination showed normal visual acuity, visual fields, and pupillary responses. Funduscopic examination of the right eye showed white material in the original segment of the inferior branch retinal artery and an embolus at the first bifurcation of the temporal branch artery (Fig. 2A). In addition, a small embolus was seen in the inferior branch of the retinal artery. Six days later, a new shiny retractile embolus was seen at the second bifurcation of the superior temporal branch retinal artery (Fig. 2B). On general examination, several toes on both feet appeared blue, and no pedal pulses were found. Cardiac and neurologic examinations were both unremarkable. Erythrocyte sedimentation rate was 34 mm/hour. A brain MRI showed extensive, chronic, periventricular ischemic changes and bilateral basal ganglia lacunes. Minimal plaque was seen by duplex ultrasound at both common carotid artery bifurcations. A TCD study and magnetic resonance angiography studies indicated moderate bilateral siphon stenoses. Transthoracic echocardiography showed left ventricular hypertrophy and mild dilatation of the aortic root and raised the possibility of debris in the aortic arch. Transesophageal echocardiography showed a large plaque 10 mm in thickness in the ascending aorta; in addition, smaller plaque formation was noted in the arch and descending aorta (Fig. 2C). A cardiac source of emboli was not found. A TCD study, performed 5 days after onset of symptoms, detected five
AORTIC ARCH Atherosomatous DISEASE

FIG. 2. Case 2. Funduscopic evaluation of the right eye (A) shows embolic material in several retinal arteries (arrows). Six days later (B), an additional shiny refractile embolus is seen (arrow). Transesophageal echocardiogram shows a plaque in the ascending aorta (C). A red colored microembolic signal is detected in the right middle cerebral artery during transcranial Doppler testing (D).

DISCUSSION

The two patients described sought medical attention because of symptoms of retinal ischemia. Transesophageal echocardiograms showed thick, presumably atherosclerotic, plaques in their aortic arches, and in both cases the embolic nature of retinal ischemia was corroborated by the observation of emboli in arterioles of the symptomatic retinas in addition to TCD microembolic signals along the distributions of the affected internal carotid arteries. These findings indicate that aortic arch plaques can be the source of embolism in the retina and can be diagnosed with ultrasound and MRI techniques.

Although severe stenoses of the cervical internal carotid artery are considered a common origin of retinal emboli, the latter can also originate from other sources. Previous reports have described external carotid artery disease (11), atrial myxomas (12), myocardial infarcts with mural thrombus formation (13), mitral valve prolapse (14), and prosthetic valves (15) as sources of embolism. Common carotid artery bifurcation and cardiac lesions were ruled out in our patients. In addition, the microembolic signals in the right middle cerebral artery during a 30-minute recording (Fig. 2D). Microembolic signals persisted a month later.

Further evaluation showed progressive renal dysfunction. A diagnosis of cholesterol embolism from aortic arch plaque with involvement of the retinal, renal, and peripheral vascular circulations was made.

finding of microembolic signals in the middle cerebral arteries on the symptomatic sides ruled out the possibility of embolism from ophthalmic artery lesions. Furthermore, Hollenhorst plaques arise from aortic or carotid atherosclerotic plaques, eliminating the possibility of a carotid source of emboli. The aortic arch has previously been suspected to be the source of retinal emboli in people with the disseminated cholesterol embolism syndrome (8,9). Cerebral, cardiac, renal, mesenteric, and peripheral vascular embolism can occur in this context (8,9,16,17). Our second patient had clinical or laboratory evidence of retinal, cerebral, and systemic embolism and illustrates the syndrome. The findings in our first patient suggest, however, that retinal embolism from aortic arch plaques can occur in the absence of clinically evident cerebral or systemic embolization. To our knowledge, this has not been recognized in previous studies. Thus, the aortic arch may be the source of isolated retinal embolism and should be studied in patients with nonrevealing carotid and cardiac evaluations.

Aortic arch atheromas have been increasingly recognized as a potential source for cerebral embolism (18). Atheromas more than 4 mm thick, particularly when ulcerated or mobile, have been associated with cerebral infarction (19). They are also predictors of recurrent vascular events and are often found in patients with cerebral infarction of undetermined cause (20). Until recently, these lesions were missed during the regular evaluation of patients with retinal or cerebral ischemia because available diagnostic tests, such as aortic angiography, were not sensitive enough to detect them. With the development of TEE as a relatively safe (21) and effective method of studying the aortic arch (22), there has been a growing awareness of the importance of evaluating this arterial segment in patients with retinal or cerebral embolism in whom carotid and carotid evaluations have been unrewarding. In our patients, TEE helped identify the source of emboli that was suspected from funduscopic examinations and TCD studies. It is to be noted that technically adequate TTE studies did not permit satisfactory imaging of the aortic arches in either of our patients. This is expected, given the limitations of the technique, and is similar to previous experience with retinal embolism (23). The superiority of TEE over TTE in detecting cardioembolic sources has been well documented, with TEE revealing an embolic source in as many as 50% of patients with a negative TTE (24,25).

Regarding the aortic arch, TTE cannot reliably image this area and often misses atherosclerotic plaques found by TEE (22). Thus, a TEE study may be indicated in the patient with retinal ischemia after a nonrevealing workup.

Transcranial Doppler ultrasound signals similar to the ones detected in our patients can correspond to in vivo microemboli composed of platelet fibrinogen, cholesterol, or gaseous material (10,26). In patients with common carotid artery stenosis these signals have been associated with cerebral ischemia, severe stenosis, and plaque ulceration (27–30). In the cases presented above, their presence identifies the link between aortic arch plaques and retinal emboli. It also indicates that microembolism is not a phenomenon of short duration; rather, it may persist for at least a month after a symptomatic event. The finding is consistent with the high risk of recurrent events in patients with large aortic arch plaques.

The aortic arch is a potential source of emboli in patients with Hollenhorst plaques. These are associated with significant morbidity and mortality. Although the risk of stroke after transient monocular blindness of all causes is approximately 2% per year (31), patients with asymptomatic retinal cholesterol emboli have an annual stroke incidence of up to 8.5% (32). The mortality rate is also increased when compared with that in age- and sex-matched control subjects (33–35) and is mostly caused by coronary artery disease and cerebrovascular disease (35). Early detection of aortic arch plaques may enable the initiation of appropriate therapy.

The optimal treatment of patients with aortic arch atheromatous embolization remains to be defined. Although some early reports suggested that anticoagulation may potentiate cholesterol embolization by preventing adequate thrombosis over the atheromatous plaque (36–38), others have reported the disappearance of mobile elements from aortic arch plaques in anticoagulated patients (39–42). This beneficial effect is most likely related to prevention of thrombus formation over an ulcerated plaque. However, anticoagulation does not exert absolute protection against platelet–fibrin embolization. Laperche et al. (43) reported recurrent embolic events in 27% of 15 patients with aortic arch plaques, despite heparin therapy. There is some evidence of stabilization of these plaques and reduction of their embolic potential with lipid-lowering drugs (44). Successful aortic endarterectomy (45) or aortic arch replacement (46) has also been reported for prevention of recurrent aortic embolization.

In summary, aortic arch plaques can be a source of cholesterol embolism to the retina and the brain. A TEE study should be considered in patients with symptomatic retinal embolism whose initial evaluations do not identify a carotid or cardiac source for embolism.

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Monocular Band Optic Atrophy

Roger E. Turbin, M.D., Leslie St. Louis, M.D., Dai Barr, F.R.C.O., and Mark J. Kupersmith, M.D.

Band or "bow tie" optic atrophy is characterized by well-described ophthalmoscopic findings in the optic nerve and nerve fiber layer and homonymous hemianopia. It is typically associated with compressive lesions of the pregeniculate prechiasmal visual pathway or, less commonly, congenital malformations affecting the postgeniculate radiations or cortex. A unique case with band optic atrophy is described because of the unilateral visual defect. The optic atrophy is strictly unilateral and without an obvious structural lesion that could explain the optic disc damage. However, incidental cerebral gray matter cortical heterotopia may mark a congenital insult that contributed to both of these abnormal findings.

Key Words: Band optic atrophy—Cerebral heterotopia—Optic tract compression.

CASE REPORT

An 11-year-old boy was evaluated for poor vision and a chronic inward-turned left eye. Three years earlier, he had been treated with a patching regimen for strabismic amblyopia. Review of records showed visual acuity of 20/40 OD, 20/160 OS, left esotropia of 8 prism diopters and "cupping," with no further details recorded about his left optic disc.

On current examination, best corrected distance visual acuity was 20/20 OD (-1.25-1.50 x 65°) and 20/200 OS (plano-1.50 x 100°). Color vision evaluated by Ishihara isochromatic plates was normal in the right eye and variable in the left, with 5/10 to 8/8 plates identified in different sets of plates. Findings in an anterior segment examination were normal. Applanation tonometry was symmetric at 16 mm Hg. The pupils were 4 mm, symmetric, round, and reactive to light. The left pupil had a sluggish consensual response to light and a moderate relative afferent defect. A motility examination revealed full versions without nystagmus, normal saccades, and concomitant left esotropia of 30 prism diopters. Ophthalmoscopy showed a tear drop-shaped right optic nerve with mild myopia-related peripapillary pigment changes and a normal nerve fiber layer (Figs. 1A, 1B). The left optic nerve had prominent band optic atrophy with loss of nasal and papillomacular nerve fibers (Figs. 2A, 2B). Peripapillary pigment changes were present but much less pronounced in the left eye. There were no other ophthalmic abnormalities in either eye. The patient had no other significant medical history. He was born full term, with no known congenital or perinatal infection. He was well developed and neurologically normal.

Visual field testing using the Humphrey 30-2 field analyzer showed the right eye field to be normal (Fig. 3A). The left eye field had dense temporal maculaparinating hemianopia with partial foveal sparing (Fig. 3B). The laboratory examination consisting of a hemogram, routine serum chemistries, and rapid plasmin reagent test produced normal results. Toxoplasmosis, rubella, cytomegalovirus, and herpes (TORCH) titers were not investigated.

Abnormal appearance on computed tomographic scan was limited to a small left optic nerve residing within a formed left optic canal, possibly smaller than the right optic canal. High-resolution gadolinium-enhanced magnetic resonance imaging confirmed atrophy of the left optic nerve from the globe to the chiasm without abnor mal signal enhancement. No mass lesion of the optic nerve, orbital apex, optic chiasm, or optic tracts was found (Figs. 4A, 4B). An area of cortical gray matter heterotopia was noted in the left centrum semiovale (Fig. 5).

DISCUSSION

Band optic atrophy is the ophthalmoscopic finding of a horizontal band of optic disc pallor, most often associated with contralateral compressive, traumatic, demyelinating, and vascular lesions or malformations of the contralateral optic tract (1,2). The disc appearance corresponds to atrophy and loss of nerve fibers that enter the disc at its nasal and midtemporal borders. Fibers entering the disc at its nasal border represent the macular temporal eye field, and fibers entering the disc temporally represent the corresponding peripheral temporal eye field. These fibers should cross in the chiasm and project to the contralateral optic tract. The appearance of the disc ipsilateral to the lesion displays a more variable degree of
FIG. 1. Color fundus photography (A) and red-free photography (B) reveal a tear drop-shaped myopic right optic disc. Mild peripapillary pigment changes are present. Although the photograph is underexposed, direct ophthalmoscopy revealed a normal nerve fiber layer.

FIG 2. Photographic technique similar to that used in Figure 1 reveals an atrophic left optic nerve in a band or "bow tie" pattern (A). Prominent loss of nerve fiber layer is detailed by red-free photography (B).

temporal pallor, often pronounced centrally and less pronounced at the disc margin, with variable loss of non-croossed nasal field fibers entering the disc at the superior and inferior arcuate zones (1). Band optic atrophy is also present as a component of the syndrome of homonymous hemiopic hypoplasia in which patients have congenital or perinatal damage to a cerebral hemisphere that results in direct damage to or transynaptic degeneration of the ipsilateral optic radiation, tract, temporal projecting nerve fibers, and contralateral projecting nasal nerve fibers (3). Band optic atrophy has not been described in association with focal cortical heterotopia.

The current case clearly involved prominent band optic atrophy of the left optic nerve. The functional correlate of loss of nerve fibers corresponding to macular and peripheral temporal eye field is indicated by the dense temporal field deficit. Visual acuity of 20/200 in this eye may also have been related to secondary strabismic amblyopia. The right optic disc was horizontally elongated, but the nerve fiber layer was robust. The normal vision, eye field, and robust nerve fiber layer support the contention that the right disc was not atrophic; rather, it was myopic. In fact, the disc area calculation by the Littmann method from fundus photographs reveals the right disc to have had an area of 3.39 mm$^2$ and the left disc an area of 2.71 mm$^2$ (4). Both were within normal limits (normal range, 2.6 ± 0.5 mm$^2$) (5). The difference in disc area calculated as 0.68 mm$^2$ was normal and would be found in at least 13% of a normal population (6). Although the absence or inconsistency of contralateral atrophic disc
FIG. 5. Coronal T2-weighted image of cerebral heterotopia (straight arrows). The lesion extends from the border of the left lateral ventricle to the gray-white matter junction. Note the asymmetrical third ventricles.

findings has been described, previous cases showed homonymous field deficits (3).

The cause of the unilateral band atrophy is unclear. A potential location of a single causative lesion includes posterior intraorbital optic nerve or selective anterior chiasm (7). However, we cannot explain how such a selective defect occurred; high resolution imaging did not identify a causative structural lesion of the right optic tract, anterior, or retrogeniculate visual pathway. Furthermore, the absence of bilateral findings suggests the lesion occurred proximal to optic tract.

Heterotopia is thought to result from insult to the embryologic radial glial fiber system and subsequent interruption of radial migration in the immature brain. Areas of incomplete migration lead to grouped composites of ectopic cells with interrupted synaptic relations. The potential for development of small focal dysplasias occurs even into the perinatal period (8). However, the extension of nodular heterotopia from the wall of the left lateral ventricle to surface cortex with normal overlying gyral pattern suggests an early insult, probably within the first 16 weeks of gestation (9). Similarly, the optic nerve, chiasm, and tract are formed by the 10th week of gestation and decussations are similar to those of the adult by 13 weeks (10). Therefore, a single embryologic insult before the 16th week could have produced cortical heterotopia and band atrophy in this patient.

In summary, this case represents a unique example of unilateral band optic atrophy without the typical findings of bilateral disc atrophy and homonymous field defects. In addition, cerebral heterotopia was present, which may serve as a marker of a more global congenital insult that interfered with the normal neural radial migration of the left cerebral cortex and may have contributed to atrophy of the left optic nerve or right optic tract. These associations have not been described in the past.

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Unusual Presentations of Sellar Arachnoid Cyst

Benjamin B. Chun, M.D., Andrew G. Lee, M.D., William F. Coughlin, M.D., David T. Floyd, M.D., and Eugene F. May, M.D.

This report describes two unusual cases of parasellar arachnoid cyst with different neuro-ophthalmologic manifestations and clinical courses: a 33-year-old woman with parasellar arachnoid cyst, manifested by incongruous homonymous hemianopia, and a 64-year-old man with a presumed parasellar arachnoid cyst and bitemporal hemianopia that subsequently decompressed spontaneously. Parasellar arachnoid cyst is uncommon, and the clinical course has been incompletely described in the literature. Optimal treatment of patients with these cysts necessitates better understanding of their signs, symptoms, and clinical course.

Key Words: Sellar—Arachnoid—Suprasellar.

Parasellar arachnoid cyst is rare, and its origin is not very well understood. It may also be confused with other pituitary cyst. This suprasellar cyst is infrequently encountered in the literature (1,2), and thus the clinical course has not been well defined. The patient's typical initial symptoms are a bitemporal hemianopic visual field defect and pituitary abnormalities (3–5). We present two unusual cases of parasellar arachnoid cyst with neuro-ophthalmologic manifestations.

CASE ONE

A 33-year-old woman had painless, progressive loss of vision and diplopia in 1987. Neuroimaging demonstrated a suprasellar arachnoid cyst. The cyst was decompressed, and the patient's vision improved. No other information is available from the surgical or postoperative period. Between 1989 and 1995, her vision was subjectively stable.

In 1996, she experienced pain when moving her eyes, diplopia, and worsening vision. Best corrected visual
acuity was 20/20 in the right eye (RE) and 20/60 in the left eye (LE). She had a relative afferent pupillary defect (LE). Visual field testing by Humphrey automated perimetry (30-2) demonstrated an incongruous, left homonymous hemianopic field defect that was denser superiorly (Fig. 1). Ophthalmoscopy showed diffuse optic atrophy in both eyes. Magnetic resonance (MR) imaging of the sella demonstrated a suprasellar arachnoid cyst compressing the optic chiasm and right optic tract (Fig. 2).

The patient underwent frontal craniotomy with fenestration of the cyst and placement of an Ommaya shunt in the cyst. After surgery, visual acuity and visual field testing showed improvement in both eyes, compared with the visual fields taken before surgery.

CASE TWO

A 64-year-old man underwent screening evaluation for glaucoma because of a positive family history. The patient reported having headaches but had no visual or other neurologic symptoms. Visual acuity was 20/25 in both eyes. Intraocular pressures were 30 mmHg OD and 24 mmHg OS. There was a right relative afferent pupillary defect. Visual fields tested by Humphrey automated perimetry (30-2) revealed a bitemporal hemianopic visual field defect (Fig. 3). Ophthalmoscopy showed a normal optic nerve in each eye.

Magnetic resonance scan of the head demonstrated a cyst within the sella turcica that extended superiorly, with upward displacement of the optic chiasm consistent with arachnoid cyst (Figs. 4 and 5).

A transsphenoidal decompression of the cyst was recommended. Before surgery, another visual field test by Humphrey perimeter demonstrated resolution of the visual field defect (Fig. 6). Repeat MR scan of the head showed that the suprasellar component of the cyst had spontaneously decompressed, with resolution of the mass effect on the optic chiasm (Figs. 7 and 8).

DISCUSSION

Suprasellar arachnoid cyst may cause visual dysfunction usually manifested as a bitemporal visual field defect. The homonymous hemianopia observed in case 1 is...
exceptional and is probably explained by anatomic variation in the relation between the dorsum sellae and the chiasm, which may result in a variety of visual deficits (6). If the chiasm is more anterior to the sella, a suprasellar cyst may encroach on the posterior aspect of the chiasm or optic tract and thus may result in a posterior chiasmal macular involving a visual field defect, such as a contralateral homonymous hemianopia. We suspect that this was the cause of our first patient’s homonymous hemianopia.

The differential diagnosis of a suprasellar cyst includes cystic craniopharyngioma, cystic pituitary adenoma, epidermoid tumor, and epithelial or Rathke’s cleft cyst. Although histologic confirmation was made from pathologic examination in our first patient, the diagnosis in our second patient was based on MR imaging characteristics. Unless histologic examination is made, diagnosis cannot be certain. However, the differential diagnosis
FIG. 7. T1-weighted sagittal magnetic resonance image shows decrease in size of suprasellar component of cystic mass. Intraseellar appearance is unchanged (arrow).

can be reasonably narrowed, using the specific MR characteristics of each cyst (7,8). Although other suprasellar cysts, such as Rathke's cleft cyst and craniopharyngioma, may manifest characteristic signals or even calcification on MR imaging, our patient demonstrated cerebrospinal isointense fluid within the cyst on all imaging sequences. This appearance is consistent with arachnoid cyst (7).

FIG. 8. T1-weighted coronal image shows resolution of the mass-effect against optic chiasm (arrow).

To the best of our knowledge, case 2 is the first suprasellar arachnoid cyst reported to undergo spontaneous asymptomatic decompression. Steinberg et al. (9) reported a case of a 47-year-old man with a Rathke's cleft cyst, which repeatedly decompressed spontaneously but which caused recurrent aseptic meningitis.

Although there are several theories in the literature concerning the genesis of suprasellar arachnoid cyst, a one-way valve theory appears most plausible (2,6,10-12). Hornig proposed that during a Valsalva maneuver, cerebrospinal fluid (CSF) could enter the sella turcica through a slit defect in the diaphragm sellae with a one-way valve effect allowing entry of CSF into the cyst and trapping the CSF within (13). We hypothesize that our patient in case 2 had a slit defect in the diaphragm sella, which consequently allowed fluid to enter with Valsalva, but without any avenue of egress. The cyst may have enlarged and stretched to the point that mechanical forces deformed or opened the valve, causing CSF to leak, thus decompressing the cyst.

The treatment options for suprasellar arachnoid cyst include observation, open surgical or stereotactic aspiration of cyst contents, or total surgical resection. Patients who are asymptomatic may be observed and, as our patient 2 demonstrated, may experience spontaneous decompression without intervention. Symptomatic patients, especially those with visual loss, may benefit from decompression.

REFERENCES

Homonymous Hemianopsia Due to a Dural Cavernous Hemangioma

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The clinical and radiographic features of extra-axial cavernous hemangiomas are described, and a case of homonymous visual field loss due to a dural-based occipital cavernous hemangioma is reported. A patient presented with a homonymous hemianopsia due to an enhancing tentorial mass lesion. The preoperative clinical and magnetic resonance imaging features were suggestive of meningioma. The patient underwent gross total resection of the lesion and the final pathologic examination was consistent with cavernous hemangioma. There was complete resolution of the visual field defect after surgery. Extra-axial cavernous hemangiomas differ from intra-axial cavernous hemangiomas in their clinical and radiographic features. The former lesions may mimic meningioma and should be considered in the differential diagnosis of a dural-based mass. Early recognition of the lesion is important because surgical removal of cavernous hemangiomas may be associated with a higher morbidity and mortality rate than meningiomas.

Key Words: Dural cavernous hemangioma—Homonymous hemianopsia.

Intracranial cavernous hemangiomas (CH) are vascular hamartomas that usually occur intra-axially within the cerebral hemispheres (1–20). Although they may arise from extra-axial locations, dural-based lesions are rare (1–20). We report a case of a dural-based occipital hemangioma that presented with a homonymous hemianopsia.

CASE REPORT

A 53-year-old white man presented with blurry vision in both eyes. Medical history was significant for removal of a malignant melanoma from his right forearm in December of 1991. Complete metastatic evaluation at that time, including bone scan, liver function tests, and chest radiograph, was unremarkable. Over the next 5 years, there was no evidence for metastatic melanoma or local recurrence. He was well until January 9, 1997, when he experienced painless blurry vision in both eyes. Ophthalmologic examination showed a visual acuity of 20/20 in both eyes. The pupils were equal in size, reacted normally to light, and there was no afferent pupillary defect. Automated visual field testing (Humphrey 30-2) revealed a right homonymous superior quadrantanopsia (Fig. 1). Slit-lamp biomicroscopy, motility examination, intraocular pressure measurements, and ophthalmoscopic examination were negative in both eyes. Magnetic resonance (MR) scanning of the head demonstrated a 2-cm lobular lesion in the left occipital area with a broad base against the inferior surface of the occipital lobe abutting the left tentorium near the midline (Fig. 2). There was heterogenous signal intensity on the double-echo and T1-weighted MR images, with relatively homogenous enhancement of the lesion after the administration of gadolinium-diethylaminoetriaminepentaacetic acid (DTPA). The tentorium adjacent to the lesion was slightly thickened and demonstrated mild homogenous enhancement. There was very little surrounding cerebral edema and only slight regional mass effect on the convexity sulci, which were slightly effaced. The radiologic diagnosis based on the MR features was meningioma. The patient was treated with oral steroids. A cerebral arteriogram was performed. The left common carotid artery injection demonstrated a hypervascular, extra-axial, dural-based mass in the region of the left tentorial incisura that was supplied by the artery of Bernasconi and Cassinari and distal branches of the occipital artery. The right common carotid artery injection demonstrated no abnormal vascularity. The left vertebral artery injection demonstrated the hypervascular mass with arterial supply from the distal branches of the posterior meningeal artery of the left vertebral artery and distal tentorial branches of the superior cerebellar artery. The hypervascularity was reticular in nature, appeared early in the arterial phase of the arteriogram, and persisted in the late venous phase. It was thought that the angiographic characteristics of the hypervascular mass were consistent with the clinical diagnosis of meningioma. The staining pattern, however, was thought to be slightly atypical in that the lesion was slightly more coarse and had a less well defined border.
HEMIANOPSIA DUE TO DURAL CAVERNOUS HEMANGIOMA

FIG. 1. Automated visual field testing (Humphrey 30-2) showed a right homonymous superior quadrantanopsia.

than that seen in typical meningioma. On January 21, 1997, the patient underwent a left combined supratentorial and infratentorial approach and gross total excision of the tentorial mass. A vascular tumor was encountered at the time of surgery. The tumor was completely excised from the dura and the margin of the tentorium was extensively coagulated. There were no postoperative complications. Pathologic examination showed multiple, thick-walled vascular channels with a thick endothelial lining consistent with the diagnosis of CH (Fig. 3). There were a few foci of lymphocytic infiltrates, old hemorrhage, hemosiderin, and extramedullary hematopoiesis. There was no evidence for cellular tumor such as meningioma. On April 11, 1997, a repeat MR scan of the head demonstrated postoperative changes and a small area of persistent enhancement near the midline of the left tentorium and adjacent incisura. A repeat automated visual field in April, 1997 (Humphrey 30-2) revealed complete resolution of the homonymous hemianopsia.

DISCUSSION

Cavernous hemangiomas are vascular malformations characterized histopathologically by abnormal collections of thin-walled sinusoidal spaces lined by endothelium and connective tissue (7). Cavernous hemangiomas usually are intracerebral tumors of the cerebral hemispheres. Cavernous hemangiomas arising from the dura are rare, but when they occur usually arise in the middle cranial fossa (3,7,8,11,12,13,17,19). Simard et al. reviewed 126 cases from the literature (1960–1986) and 12 additional cases of histologically confirmed CH (19). Of these cases, 13 were extra-axial in the middle cranial fossa, 4 were in the cerebellopontine angle, and only 1 was in association with the tentorium (19). Nambu in 1983 reviewed the world literature on CH and reported only 23 cases of extracerebral CH of the middle fossa (13). In this review, 10 patients (44%) demonstrated ocular symptoms or signs, including diplopia, anisocoria, visual acuity loss, visual field defects, or ocular motor cranial neuropathy (13). McCormick and Butler reviewed nearly 500 vascular malformations of the central nervous system and reported 2 asymptomatic cases of CH of the tentorium cerebelli and mentioned 3 other cases from the German and Italian literature (10). Other CH have been reported in the cavernous sinus (7,8,13,17), cerebellopontine angle (1), internal auditory canal (20), Meckel’s cave (2), cava du spinal (14), cranial nerves (9), peripheral nerves, optic nerves and chiasm, within the ventricular system (4), anterior cranial fossa (3), and tentorium (12,16,18). Among the extra-axial sites, the large number of cases reported in the cavernous sinus (7,8,3,17) may suggest a predilection for this location.

Extra-axial CH differ clinically and radiographically from intra-axial CH (1–20). Meyer et al. emphasized that despite similar pathologic features, these two entities are clinically distinct (11). These authors argued that extra-axial CH demonstrated features suggestive of neoplasm, including mass effect, encasement of neurovascular structures, growth in pregnancy, and radiographic features suggestive of tumor. In fact, unlike intra-axial CH, the clinical and radiologic features may mimic meningioma before surgery (7,15,17). Meyer et al. reported eight extra-axial CH, of which six arose from the cavernous sinus, one from the petrosal sinus, and one from within the torcular Herophili. The preoperative diagnosis was meningioma in seven of these eight patients (11).

Isla et al. reported a large CH of the dura in the anterior fossa of a pregnant woman (3). The lesion resembled a meningioma and was difficult to remove because of marked vascularity and profuse bleeding after minimal incision of the capsule (3). Perry et al. reported a 77-year-old woman with partial seizures due to an enhancing dural-based parietal convexity mass. Although the preoperative appearance on computed tomography (CT) scan suggested meningioma, the pathologic findings were typical of a dural CH (15). Saldana et al. reported a neonatal CH of the dura matter and reviewed the literature on congenital CH (18). Quattrinchi et al. reported a CH of the tentorium cerebelli and reviewed six other cases from the literature. Of these seven cases, two presented with headaches, one with congenital hydrocephalus, and four were asymptomatic (16). Our patient presented with a homonymous visual field defect.
Computed tomography scans of extracerebral CH usually demonstrate isodense or hyperdense lesions with homogeneous contrast enhancement (16). The CT findings may be variable, however. Moritake et al. demonstrated an unusual pattern of annular enhancement surrounding a high-density mass with calcification in a neonatal tentorial CH (12). The CT pattern of dural CH may be indistinguishable from that of meningioma. Unlike meningi-
FIG. 3. Pathologic examination revealed multiple, thick-walled vascular channels with a thick endothelial lining. There were a few foci of lymphocytic infiltrates, old hemorrhage, hemosiderin, and extramedullary hematopoiesis.

oma, however, the lesion does not typically show calcification, and the surrounding bone may demonstrate erosion or remodeling rather than hyperostosis (5,7). Calcification and bone changes were not present in our patient, but our patient did not undergo a CT scan.

The MR signal characteristics of extra-axial dural CH differ substantially from the typical MR features of intra-axial CH. The MR features of intra-axial CH include 1) isointense or hypointense signal on T1-weighted images; 2) hypointense or hyperintense signal on T2-weighted images; 3) a prominent hypointense rim on T1- and T2-weighted images that may represent hemosiderin-laden macrophages; and 4) nonhomogenous enhancement after gadolinium-DTPA administration. Extra-axial CH, on the other hand, often are homogeneously isointense or hyperintense on T2-weighted images and enhance markedly and homogeneously after gadolinium-DTPA (5,7). This MR appearance may be identical to that of meningiomas. Quattrocchi et al. reported the MR findings of a tentorial CH (16). The lesion was well circumscribed and had low signal intensity on T1-weighted images, a high signal intensity on T2-weighted images, and homogeneous enhancement with gadolinium-DTPA. Similar MR signal characteristics have been demonstrated for CH in other extra-axial locations (e.g., cavernous sinus) (5,7,8). In our patient, the preoperative diagnosis based on the MR features was meningioma.

Cerebral angiography may or may not be useful in distinguishing CH from meningioma. Cerebral angiography in tentorial CH may demonstrate no abnormalities, an avascular mass, or a fine arterial, capillary, and venous tumor blush (5,7,8). In our patient, the angiographic findings were thought to be consistent with a meningioma.

In most cases, the diagnosis of CH cannot be made until the time of surgery. The correct diagnosis is important because of the higher risk of morbidity and mortality after removal of these vascular lesions (3,13). Although surgical therapy has been the mainstay of therapy for CH, surgical resection of vascular, extra-axial, dural CH may be difficult because of intraoperative bleeding. Namba et al. reported a 38% mortality rate with only three complete resections for extra-axial CH (13). Nevertheless, complete excisions of dural CH have been reported (15). Our patient underwent successful resection without intraoperative or postoperative complications and with complete resolution of the preoperative homonymous hemianopic visual field loss. Significant blood loss was not encountered in our patient, and no blood transfusion was required. Preoperative endovascular embolization or radiation therapy have been suggested by some authors, but remain controversial (3,5,7,8). Our patient did not undergo embolization or radiation therapy.

Unfortunately, the terminology regarding vascular lesions of the central nervous system (CNS) in the literature is confusing because of inconsistent and imprecise usage. The current case draws particular attention to the terms “angioma” and “hemangioma.” Intracranial CNS vascular malformations composed of vascular channels that are devoid of intervening neuroglial tissue are correctly termed “cavernous angiomas.” Central nervous system cavernous angiomas are usually low-flow lesions that may be safely removed surgically. These lesions also lack intervening mesenchymal tissue, in contrast to the benign vascular tumor known as CH. Cavernous hemangiomas consist of capacious vascular channels separated by variable amounts of fibrous or myxoid connective tissue. The CH bears a close relationship in age and anatomic distribution to the more common capillary hemangioma. Cavernous hemangiomas may include superficially located components of capillary hemangioma, but unlike the pure capillary hemangioma, which tends to regress by sclerosis with age, CH may spontaneously slowly enlarge and may exhibit accelerated growth during puberty or pregnancy. Surgical excision of CH may result in catastrophic hemorrhage. The cavernous angioma and CH also possess distinguishing genetic and syndromic associations. The familial form of cavernous angioma in Hispanic Americans has been mapped to a locus on chromosome 7 and traced to a common Mexican ancestor. Cavernous hemangiomas, on the other hand, may be associated with the Maffucci syndrome, blue rubber bleb nevus syndrome, or Kasabach-Merritt syndrome (21-23).

The lesion that we describe in this report is a CH of the leptomeninges. Meyer et al. believed that the term “cavernous hemangioma” was a misnomer for extra-axial CH and suggested that the term “sinus cavernoma” was more appropriate (11). We believe that these new terms do not contribute to diagnostic clarity.

To our knowledge, this is the first case of extra-axial tentorial CH involving the occipital lobe and presenting as a homonymous hemianopsia. Cavernous hemangiomas should be considered in the differential diagnosis of dural-based mass lesions. The clinical and radiographic features of dural CH may mimic meningioma, and accurate diagnosis is crucial to avoid unnecessary surgical morbidity and mortality. Extra-axial CH are clinically and radiographically distinct from intra-axial CH, and may represent a distinct clinical entity.
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References


When Fighting Makes You See Black Holes Instead of Stars

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A young boxer developed a left homonymous hemianopia immediately after a blow to the head. A magnetic resonance image showed a lesion in the right lateral geniculata region that was consistent with a previous cerebral hemorrhage and was likely the cause of the visual field defect.

Key Words: Homonymous hemianopia—Traumatic brain injury—Lateral geniculate body.

CASE REPORT

A 19-year-old boxer came to the Cleveland Clinic Foundation with difficulty seeing in the left hemifield. The patient was otherwise healthy and took no medications. He had no ocular medical history. He was a competitive boxer and during a fateful fight was stuck hard in the head by a right hook. After getting up slowly from the mat, he noted that the left side of his vision seemed different and he had trouble seeing his opponent.

His neurologic history was of interest in that approximately 2 years before this injury, the patient had awakened with a numb sensation in his left foot. During the next 6 months, the sensation had proceeded up to the level of his mid left thorax. The patient sought the opinions of a neurologist and an ophthalmologist before presentation for his visual loss and neurologic symptoms. He had two cerebral magnetic resonance imaging scans and he was thought to have suffered a stroke. However, no explanation could be offered for the incongruous left homonymous hemianopia that he showed on visual field testing, because the stroke seemed to be isolated the posterior thalamic region and did not involve the optic radiations or any visual cortical components. Similarly, likewise, no explanation could be offered for the neurologic symptoms. Evaluation for his sensory symptoms included a lumbar puncture that yielded normal spinal fluid results including a normal Tourtellotte’s analysis and the absence of oligoclonal bands; no cervical magnetic resonance image (MRI) was obtained.

When seen at the Cleveland Clinic 1 month after the initial injury, his visual acuity was 20/20-2 OD and 20/20 OS without correction. Pupils were 5 mm with equal reactions, and he had no afferent pupillary defect. He was orthophoric at distance without correction. Versions were full in both eyes. Confrontational testing of visual fields showed a defect consistent with left homonymous inferior quadrantanopsia. Applanation tonometry readings were 14 in both eyes. Slit lamp findings were unremarkable. The optic nerve heads were found to have temporal pallor OU. The remainder of the dilated fundus examination yielded findings within normal limits. Neu-

![FIG. 1. Goldman visual fields showing mildly incongruous left homonymous hemianopia.](image-url)
FIG. 2. Humphrey visual field showing complete left homonymous hemianopia.

FIG. 3. Axial T2-weighted magnetic resonance image sections: (A) Area of encephalomalacia in the region of the right lateral geniculate body (arrow), (B) axial pathologic section of the brain (taken from Melville and Hanaway, Atlas of the Human Brain, Philadelphia: Lea & Febiger, 1970) with arrow identifying the lateral geniculate nucleus, and (C) a more dorsal section showing encephalomalacia of the right thalamic region (arrow).
Geniculate Hemorrhage Due to Closed Head Trauma

FIG. 4. Humphrey visual field showing incongruous left homonymous hemianopia.

Reinterpretation of the scans revealed an area of encephalomalacia in the right posterior thalamic region; however, this abnormality extended inferiorly into the lateral subthalamic region and involved the lateral geniculate region, accounting for the visual field abnormalities (Fig. 4).

The patient was thought to have had a traumatic right lateral geniculate hemorrhage during a competitive boxing match. He was further thought to have a lesion of the T6 spinal cord level, most consistent with a demyelinating lesion, probably unrelated to his ocular findings. However, no spinal cord mass or signal consistent with demyelination was identified on subsequent imaging.

This case illustrates a rare lateral geniculate hemorrhage induced by closed-head trauma.

Variability in Visual Cortex Activation During Prolonged Functional Magnetic Resonance Imaging

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This study was conducted to test whether cortical activation varies across successive epochs during functional magnetic resonance imaging (fMRI) studies. Ten normal adult volunteers were studied with a 1.5-T MR scanner. Pseudorandom study planes were chosen perpendicular to the tentorium cerebelli, at two thirds the distance from the posterior edge of the splenium of the corpus callosum to the transverse sinuses. Functional images were acquired with a T2*-weighted spoiled gradient echo sequence. The visual cortex was stimulated by goggles flashing at 8 Hz. Each study consisted of 92 sequential scans, lasting 15 seconds each for a total of 20.5 minutes. Two scans without stimulation were alternated with two scans of visual stimulation. Scans 3 through 83 were divided into five sequences of 16 scans. For each sequence, the number of pixels within a predefined rectangular region of interest that showed increased activity during stimulation were counted. Least squares regression models of straight lines were fit to the data. The initial level of visual cortex activation in the region of interest, as measured by the y-intercept, varied substantially from subject to subject (range: 4-68, p < 0.001). There was sufficient evidence of systematic change with time to reject the hypothesis of constant activation with the same stimulus over time (p = 0.03). The observed visual cortex activation with single-plane fMRI varied both with time over successive epoques and among subjects. Possible factors responsible for the variation may include head movement, eyelid position, attention, and physiologic fatigue. These factors must be accounted for in experimental design and in data analysis and interpretation.

Key Words: Functional magnetic resonance imaging—Visual cortex.

Functional magnetic resonance imaging (fMRI) is rivaling positron emission tomography (PET) and single photon emission computed tomography (SPECT) in the ability to provide functional neuroanatomic information. Additionally, fMRI is nonionizing and noninvasive, allowing repeated testing without exposing patients to radioactive substances (1). fMRI has already proved to be a highly valuable research and clinical tool. Several investigators have used it to study striate (2-6), extrastriate (7), motor (8) and auditory cortices (9), and language lateralization (10) in humans.

Gadolinium (11) was used in one of the first successful fMRI studies of visual cortex, but subsequent investigators have used blood oxygen level-dependent contrast (12) to identify areas of cortical activity in gradient-echo MR images. Neuronal activation is associated with an increase in local blood flow (13) and volume with little or no change in oxygen consumption (14). The resultant increase in venous oxygenation causes an increase in MR signal (14). During fMRI, blood oxygen level-dependent studies, two sets of magnetic resonance images are acquired, one set during a functional activity ("on"), and the other with the patient resting ("off"). The sets are compared to identify any changes suggestive of an increase in local blood flow associated with brain activation (15).

Ordinarily, on and off sets are alternated during a single fMRI study, which usually lasts just a few minutes. In more complex studies (cognitive studies, e.g.), several functional activities may be performed over a more extended period. One group of investigators (16) demonstrated the "feasibility and value of conducting multiple functional paradigms in single sessions." Because of the important methodologic implications, several investigators have studied visual cortex activation during prolonged sustained stimulation, and the results have been inconsistent (17-19). We studied the stability...
of visual cortex activation in a different manner, over successive epochs, because ordinarily, on and off sets are alternated during single fMRI studies.

METHODS

Ten normal adult volunteers were studied (age range, 22-35 years). Two were women, and eight were men. Subjects were placed supine in a 1.5-T MR scanner (Siemens Magnetom Vision; Erlangen, Germany). Closely fitting foam pads were placed around their heads to discourage movement.

Task

Visual stimulation was obtained by using light-proof binocular goggles with a 5 x 5 array of red light-emitting diodes flashing at 8 Hz (model S10VSB-10: Grass Instruments; Quincy, MA). Subjects performed the passive task of lying in the MR with goggles over the eyes. They were instructed to keep the eyelids open during the stimulation periods, but eyelid position was not monitored. The subjects were told to stay awake throughout the session. To ensure compliance, they were given the active task of squeezing a rubber ball each time the lights were turned on. The ball was connected by a rubber tube to a bell in the monitor's room. In this way, it was confirmed by the monitor that all subjects remained awake throughout the study.

Imaging Method

Several research groups have used a plane through the calcarine fissure to study visual cortex activation (11). We found this to be an unreliable and inconsistent method for several reasons: First, the calcarine fissure is rarely flat and commonly bends at least once ventrally or dorsally. Second, frequently, there is interhemispheric asymmetry in the position of the left and right fissures. Third, there is wide intersubject difference in the first and second variables. The combination of these factors made imaging the visual cortex in one plane a difficult task, and the amount of visual cortex included in the plane varied from person to person.

Instead, in an attempt to obtain anatomically consistent views across volunteers, each was studied with pseudocoronal planes. T1-weighted parasagittal scout images (recovery time [TR], 300 msec; echo time [TE], 15 msec; alpha, 90°; matrix, 256 x 256; slice thickness = 5 mm) were obtained for anatomic localization. Another T1-weighted image was obtained in a pseudocoronal plane perpendicular to the tentorium cerebelli, two thirds the distance from the posterior edge of the splenium of the corpus callosum to the transverse sinuses and was labeled the pseudocoronal anatomic image (Fig. 1A). This method insured that the plane was posterior to the parieto-occipital sulcus.

For the activation studies, an oblique 5-mm thick axial slice was aligned in the same position as the pseudocoronal anatomic image. The functional images were acquired with a T2*-weighted spoiled-gradient echo sequence (TR, 100 msec; TE, 60 msec; alpha, 30°; matrix, 128 x 128; and field of view [FOV], 22-24 cm). Shim-
mig of the scanner occurred before the functional studies for each subject.

Each study consisted of 82 sequential scans, lasting 15 seconds each, for a total of 20.5 minutes. The sequence alternated two scans (30 seconds) of no activation (resting baseline) with two scans of activation (flashing lights in both eyes simultaneously), for 20 periods of active and resting states. To study the possibility that our results could be caused by instrumental factors, the experiment was also performed with a phantom.

Data Analysis

All images were transferred to a commercial system (Sun SPARC station I Sun Microsystems; Mountain View, CA). The first two images were discarded to ensure that a steady state had been achieved. For each subject, five activation maps were calculated using successive sets of 16 images. Visual inspection of the images displayed rapidly was performed. In addition, the centroid of each image was calculated and plotted versus time to monitor movement in the x- and y-planes. The area of each image was calculated and plotted versus time to gauge through-plane movement. No motion correction was performed on the data set.

An image processing routine written in IDL (Interactive Data Language; Research Systems; Boulder, CO) created a statistical parametric map. To calculate the statistical parametric map, the baseline images and the activated images of the time course of the functional images were divided into two groups and subjected to Student's t-test on a pixel-by-pixel basis. The threshold value was chosen by calculating the 1% significance level for all 80 images of each patient using the processing strategy described by Requardt (20).

Within the pseudocoronal anatomic T1 images, a rectangular region of interest (ROI) containing calcarine cortex in both hemispheres was selected for each subject (Fig. 1B). The ROIs were determined anatomically without reference to activation. Control ROIs of identical size were selected from the cerebellum. For each statistical parametric map, the number of pixels with t-values above the threshold of p = 0.01 were counted within the ROI (Fig. 1C). Least squares regression models of straight lines were fit to the data to evaluate the relationship between the level of activated pixels in the ROI and the time since the beginning of the testing session. The regression models that were evaluated included i) a separate intercept and a separate slope for each subject, ii) a separate intercept for each subject and a common slope for all subjects, and iii) a common intercept and common slope. F-tests comparing the residual variance from alternative models were used to test whether additional parameters (individual slopes or intercepts) should be included (21).

RESULTS

Review of plots of the level of activated pixels versus time showed substantial variation among volunteers (Fig. 2). Comparison of the three statistical models of the data showed two important features of the response pattern of the 10 participants: First, the overall level of activation,
characterized by the y-intercept, varied significantly among participants ($p < 0.001$), ranging from 4 to 68 pixels in the ROI with a mean of 34. Second, a unique slope for each person did not provide a significantly improved fit of the data compared with the fit of a common slope for all participants ($p = 0.29$). In some volunteers, the slope was positive, and in others it was negative. In all 10 volunteers, there was little or no activation in the cerebellum. These comparative data suggest that the blood oxygen level-dependent signal changes in the visual cortex truly represented stimulus-related cortical activation and were not artifactual.

In the phantom experiment, no consistent grouping of the (approximately 1%) of pixels above the threshold occurred. This confirmed that our data genuinely reflected a change in activation of visual cortex and that there was no machine variability that could account for it.

Slight head motion was detected in all volunteers. The average range of motion of the centroids in the $x$ direction was 0.83 mm (range, 0.53–1.12 mm), whereas the average range of motion of the centroids in the $y$ direction was 2.1 mm (range, 1.03–2.84 mm). The average change in image area, reflecting through-plane movement, was 4.2% (range, 1.5–8.8%).

**DISCUSSION**

In our single-plane study, visual cortex activation varied across successive epochs when volunteers stimulated with flash goggles were studied using fast low-angle shot (FLASH) fMRI. Results of the studies of previous groups have been contradictory. Hathout et al. (17) performed uninterrupted visual stimulation by flash goggles for 18 to 24 minutes and found a decrease in signal intensity in visual cortex 2 to 5 minutes after the initial peak in activation. In another study by Kranda et al. (18) when subjects viewed flashing vertical gratings for 4 minutes, there was an immediate increase in signal measured in visual cortex, followed by an exponential decline for the remaining stimulation period. In contrast, Howseman et al. (19) found stable activation by checkerboard stimuli using echo-planar and FLASH techniques, and they suggested that discrepancies in results may be caused by the use of different stimuli and not by the imaging method.

Although the use of flash goggles, rather than checkerboard stimuli, may have accounted for a change in
activation, there are several other explanations that must be considered, including head movements, habituation of cortical neurons, varied attention to the stimulus, and eyelid position.

Head movements may have accounted for the signal variation in our study. Although the cine loop can detect large head movements within the plane of the image, small movements may be missed. Our analysis of the centroid position and image area over time suggested that some slight head movements occurred. Motion correction algorithms currently exist, but these are more applicable to three-dimensional data sets.

Retinal photoreceptors (22) and neurons in the lateral geniculate nucleus (23) do not fatigue during continuous light stimulation. However, in animals, intracellular recordings have demonstrated that striate cortical neurons can adapt during prolonged viewing of high-contrast sinusoidal gratings (24). In visual evoked potential studies in humans performed over several minutes or hours, the P100 latency and amplitude can remain relatively stable (25), but in some instances a decrease in the amplitude can be observed with passing time (26).

Alternatively, changes in level of activation may be explained by variable attention to the visual stimulus. Hypervigilance may have accounted for the increase in activation seen in three of our volunteers, whereas decreased attention during the task in the other volunteers may have resulted in a decrease in activation. Participants in other studies (19) tested with a checkerboard pattern, perhaps a more interesting stimulus, may have had stable activation with passing time because they were more attentive during the prolonged study.

Changes in eyelid position may also have accounted for some of the signal variation. Although subjects were instructed to keep their eyes open during the visual stimulation periods, we had no way of monitoring this.

In addition, the interpersonal variability in the amount of visual cortex activation was striking. It is possible that variable activation is a real phenomenon, but anatomic variation in striate cortex is likely a contributory factor. Our pseudocoronal planes produced more consistent images through visual cortex than axial planes would have allowed. However, we still could not guarantee that exactly the same portion of striate cortex was imaged from subject to subject. Ross et al. (27) demonstrated differences in visual cortex activation in younger versus older
Variability in visual cortex activation, for which there are several possible reasons, must be accounted for in fMRI experimental design and in data analysis and interpretation. Quantitative intersubject comparisons and those of visual tasks performed at the beginning and end of long study sessions may not be valid. Every attempt must be made to reduce head movements. Acquiring the data in three-dimensions is more desirable to allow the application of motion correction programs. Interleaving data in three-dimensions is more desirable to allow the application of motion correction programs. Interleaving visual tasks during prolonged stimulation periods, and whether variation in visual attention may alter the level of fatigue during a lengthy study session. Future investigation should include comparison of flash and checkerboard stimuli during prolonged stimulation periods, and whether variation in visual attention may alter the level of cortical activation. Finally, a method for insuring that the eyelids remain open during the stimulation periods should be applied.

REFERENCES

Visually Induced Reactivity in Posterior Cerebral Artery Blood Flow

Babette Spelsberg, M.D., Andrea Böhnning, M.D., Detlef Kömpf, M.D., and Christof Kessler, M.D.

To evaluate visually induced reactivity (VIR) in the posterior cerebral artery (PCA), mean flow velocities in the PCA were measured bilaterally in 35 normal subjects and in 17 patients with PCA territory infarctions, by means of transcranial Doppler ultrasound. After the individual PCA baseline flow was estimated, different visual stimuli were applied: on-off light, colored light, complex scene, and visual imagery task, and the CO2 test was administered. A sampling rate of 20 Hz was used, and the raw data were transferred to a computer. The baseline flow and the maximum flow increase were calculated with a specially designed program. In control subjects, the on-off light stimulus induced a mean increase in PCA flow velocities of 21.5 ± 6.4%, and colored light induced an increase of 22.3 ± 6.3%. Complex scenes significantly elevated VIR more than light and colored light, with a mean increase of 28.8 ± 6.8% (p < 0.05). Mental imagery had no significant effect on PCA flow velocities. There was no significant difference in flow between the right and left PCA in healthy subjects. In patients with PCA territory infarctions with homonymous hemianopsia or quadrantanopsia, there was a marked decrease of VIR and CO2 reactivity on the affected side corresponding to the extent of PCA territory infarction. Visual stimuli increased blood flow velocity bilaterally in the PCA, which supply the visual cortex and visual association area. This noninvasive test seems to be well suited to normal subjects and to patients with vascular disorders affecting the PCA.

Key Words: Brain metabolism—CO2—Posterior cerebral artery territory infarction—Transcranial ultrasound—Test—Visual stimulation.

Cerebral blood flow (CBF) depends on the state of brain activation and ranges between 40 ml per 100 mg brain tissue per minute at rest to 125 to 135 ml per 100 mg brain tissue per minute at excitation (1). Positron emission tomography studies (2,3) have demonstrated that visual stimulation differentially increases local metabolism in the visual cortex as a function of stimulus complexity. In hemianopic patients the local cerebral metabolic rate for glucose is reduced in the visual cortex (3).

Transcranial Doppler sonography (TCD) has also been used to investigate the dynamics of cerebral blood flow by recording flow velocities in the basal cerebral arteries. This method has the advantage of excellent temporal resolution (4,5). Aaslid (6) was the first to study the dynamics of cerebral blood flow in the posterior cerebral artery (PCA) in response to stimulation with light. A study by Urban et al. (7) showed that occipital lobe infarctions of different degrees of severity limit the visually activated blood flow increase in the ipsilateral PCA.

It is well known that blood flow reactivity to visual stimulation is specific to the PCA supplying the visual cortex (6–8). A small increase in blood flow in the middle cerebral artery (MCA) caused by visual stimulation has also been noted, but this increase does not exceed 7% (standard deviation ranges between 3% and 8%) and is likely to be based on nonspecific effects, such as attention and arousal (6–8).

Acute hypercapnia induces immediate acidosis of the cerebrospinal fluid and brain cells. The direct effect of CO2 and acidosis is dilatation of muscle cells of the cerebral arterioles, which increases cerebral blood flow (9). Single photon emission computed tomographic studies and reports on patients with various brain lesions (10–13) show that left inferior occipital regions play a prominent functional role in visual mental imagery. Because the left inferior occipital cortex consists mainly of the primary and secondary visual cortices, and because the PCA is the source of its blood supply, we tested whether a visual imagery task would increase blood flow velocity in the left PCA.

We wanted a detailed evaluation of the visually induced reactivity (VIR) of blood flow in the PCA in response to different visual stimuli, visual imagery tasks, and CO2 stimulation in normal subjects and in patients with PCA territory infarctions. The objective of our study was to investigate whether the increase in flow velocity during activation is correlated with the complexity of the applied stimulus and whether a reduction of VIR occurs in patients with PCA infarctions.
SUBJECTS AND METHODS

We used as controls 19 young subjects with a mean age of 24.3 ± 1.5 years. Among these were 10 men and 9 women with no sign of cerebrovascular or ophthalmologic disease. Some subjects had myopia and wore their glasses during VIR measurements. To test whether VIR is age dependent, a second group of 16 older subjects with a mean age of 54.9 ± 11.9 years was investigated. These patients were recruited from the neurology inpatient clinic. They showed no signs of cerebrovascular disease or dementia. Visual acuity was normal, assessed by reading from a chart.

Patients with PCA Territory Infarctions

Seventeen patients with PCA territory infarctions (mean age, 60.2 ± 11.9 years) were included in our study. All had hypodense lesions in the occipital region, revealed by cranial computed tomographic scan. Ten patients had complete homonymous hemianopsia, and seven had quadrantanopsia. Ten PCA territory infarctions were on the right side, and seven were on the left side. Two patients with bilateral PCA territory infarction were not included in the study because the intent was to compare the nonaffected side with the affected side. In eight patients the examination was performed within 4 weeks after the stroke, and in the other nine patients the interval between stroke and examination was approximately 2 years.

Experimental Setting

Studies were carried out in a dark and quiet room. Subjects sat comfortably and relaxed in a chair and looked at a screen 2 m in front of them on which the different visual stimuli were presented. They were asked to keep their eyes closed between the tasks and to open them for stimulation. To minimize artifacts induced by the environmental setting, the laboratory was absolutely dark, and the projected slide stimuli occupied approximately 80% of the visual field. The remaining 20% was occupied by the surrounding dark room. There was no conversation during the measurements except for short commands to open or close the eyes. The TCD recordings were taken from the left and right PCA, successively. The conditions of the experiment were the same for all participants.

A TCD device (TC 2000S; EME GmbH, Überlingen, Germany) was used, with a 2-MHz probe. The ultrasound intensity was 100 mW/cm², and the sampling rate was 20 Hz. A durable probe was installed, and the intracranial PCA was insonated through the transtemporal window. The MCA was identified at a depth of 50 mm. Then the probe was turned to a backward position, and the MCA was insonated at a depth of 62 ± 2 mm, based on the characteristic velocity spectrum and specific response to light stimulation. One young subject screened for participation could not be included because the transtemporal window on the left side could not be obtained. In all other participants the characteristic velocity signal of the PCA was found. Flow velocities were measured continuously with subjects at rest. These constant values formed the individual baseline flow velocities. Different stimuli were then applied:

- On-off light: After a rest phase with closed eyes, the slide projector was turned on with no slide for 25 seconds, and the subjects were asked to look at the lighted screen.
- Colored light: Red, blue, or green was projected on the screen for 25 seconds, and the subjects were asked to look at it.
- Complex scene: A landscape scene was projected on the screen for 25 seconds.
- Visual imagery task: The subjects were asked to imagine a scene, preferably from their last holiday, or any other scene as vividly as possible for 40 seconds with their eyes closed.

Light intensities of the different visual stimuli were assumed to be constant because the same slide projector was always used. All stimuli were applied after the flow velocities had reached baseline.

In addition to the VIR measurement, vasomotor reactivity of each PCA was estimated by the CO₂ test. The subjects breathed a mixture of room air and 33% O₂ through an anesthesia mask. The mean flow velocity in the PCA was measured for several minutes, and the baseline flow velocity (V₉) was calculated. Then, CO₂ was continuously added until an end-tidal CO₂ concentration of 8% was obtained. At this point the maximum flow velocities (V₉ₘₐₓ) were recorded, and the cerebral vasomotor reactivity was calculated as follows:

\[ V₉ₘₐₓ\% = \left(\frac{V₉ₘₐₓ - V₉}{V₉}\right) \times 100 + V₉ \]

These results were compared with the percentage increase of PCA flow velocities after visual stimulation.

During visual stimulation, flow velocity values were recorded continuously, and the raw data were stored for later evaluation. The data were calculated by the standard algorithm implemented on the Doppler device and exported to an ASCII file. We designed a program in Turbo Pascal (Borland Int., Scotts Valley, CA) for further data processing. First, a running average was calculated from the data. Then the increase in blood flow velocity was analyzed. If it exceeded 12% of the baseline flow, the average of the following 70 values was interpreted as the maximum value. This threshold was established to allow measurement of the specific visual effects, because it is known that the nonspecific effects such as attention and arousal lead to an increase in blood flow velocity of up to 7%. To be on the safe side, another 5% was added, which was approximately one standard deviation. The difference between baseline and maximum flows was used for calculation of percentage of blood flow increase.

Because a relatively small sample was studied and because the data were calculated as percentages rather than absolute numbers, a normal distribution was not expected. The Kolmogorov–Smirnov test results confirmed this assumption. Therefore, nonparametric procedures were used for data analysis. The Wilcoxon matched pairs test was used for comparison of the different stimuli within the study samples. The Mann–
Whitney test was applied to compare the same stimuli among the different groups. The data are expressed as mean percentage increase ± standard deviation.

**RESULTS**

**Control Subjects**

In the control subjects, baseline blood flow of the PCA was $34.2 ± 6.4$ cm/sec in the older subjects and $38.0 ± 5.5$ cm/sec in the young subjects. This difference was not significant. The young and older normal subjects also showed no significant differences in VIR, visual imagery task and CO2 tests. As a result, they were treated as one group for further evaluations (Table 1). The on-off light stimulus increased blood flow velocities by $20.4 ± 5.9\%$ in the left and by $22.5 ± 6.9\%$ in the right PCA. Colored light increased blood flow velocities by $20.6 ± 6.8\%$ on the left and by $23.9 ± 5.8\%$ on the right side. There was no significant difference between these stimuli ($p > 0.05$). Complex scenes produced a significantly higher increase in blood flow velocity of $28.9% ± 6.7%$ in the right and $28.6 ± 6.9%$ in the left PCA ($p < 0.05$) compared with increases with on-off light and colored light.

Visual imagery had no significant effect on PCA flow velocities, compared with non-visual-induced fluctuations of blood flow during the resting phase. In response to flow velocity with the imagined scene, there was either a slight increase or no change in blood flow velocity.

Stimulation with CO2 increased PCA blood flow velocities by $58.3 ± 9.5\%$. There was no significant difference between the right or left PCA.

**Patients With PCA Territory Infarctions**

In patients with PCA territory infarctions, baseline flow velocities on the affected side did not differ from values on the nonaffected side (Table 2). In patients with complete homonymous hemianopsia, no significant VIR could be measured on the affected side (Table 2). There was only one exception, a 77-year-old patient with a right-side PCA territory infarction and complete homonymous hemianopsia. In this patient, VIR to all stimuli presented on the affected side was comparable to that on the nonaffected side.

As in the control groups, visual imagery produced no significant increase on either side. In these patients CO2 reactivity of the affected PCA was reduced to $30.4 ± 12.5\%$, which was $50\%$ of the normal response on the nonaffected side. Patients with quadrantanopsia showed a reduced VIR only with the first two stimuli, compared with VIR in the nonaffected side ($p < 0.05$), where CO2 reactivity was reduced to $39.6 ± 20.1\%$, which corresponds to a reduction of $26.5\%$ compared with the normal response. A summary of the results is shown in Figure 1.

**DISCUSSION**

Functional activation of the brain is coupled with a local increase in cerebral blood flow (14–16), which is probably metabolically mediated by adenosine, $K^+$ and $H^+$ (9). We investigated VIR of normal control subjects and patients with occipital lobe infarction and found in normal subjects an association between the increase in blood flow velocity and the complexity of the visual stimulus. In patients with PCA territory infarction, however, we found significantly reduced reactivity, corresponding to the extent of brain damage: The more extensive the tissue damage, the greater the reduction in VIR and CO2 vasomotor reactivity. There was no reaction to visual imagery in control subjects or patients with PCA territory infarctions.

In positron emission tomography studies, Phelps and Mazziotta (2) and Phelps et al. (3) reported an increase in brain glucose metabolism in the primary visual cortex (PVC) and in the visual association cortex in response to differing complexities of the visual stimuli. Our findings based on TCD measurements were, in principle, the same. The complex scene stimulus significantly increased flow velocity more than did the color and on-off light stimuli. This has been shown by the TCD study of Conrad and Kingelhoff (17) who also found a significant increase in blood flow velocity in the PCA after complex visual stimulation. Sitzer et al. (18) found an increase in blood flow velocity that was comparable to our results ($30.4 ± 6.4\%$) in the PCA using TCD while showing a complex color video film. This can be explained by the lower informational content of the simple light and color stimuli. These stimuli should therefore mainly activate the PVC, whereas complex stimuli containing much information about shapes, perspective, or meaning of a scene additionally activate the association cortex. Because TCD-VIR measurement of the PCA involves invasion of the PCA main branch, activating both the primary visual cortex and the visual association cortex, these vessels cannot be investigated separately. Phelps and Mazziotta (2), however, reported an increase in glucose metabolism of $12\%$ in the PVC and an in-

<table>
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<th>TABLE 1. Controls: baseline flow (cm/s), mean percent increase in blood flow velocity (%) and standard deviations in response to various stimuli in normal subjects</th>
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<tr>
<td>Baseline flow</td>
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<tr>
<td>Right PCA</td>
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<td>Left PCA</td>
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**PCA, posterior cerebral artery.**

$^{1/2} = p < 0.05$ compared with on-off light, $^{3} = p < 0.05$ compared with color, $^{1/2}$ and 3 $= p < 0.01$ compared with on-off light and color.
crease of 6% in visual association cortex in response to white light, whereas a complex scene produced an increase of 45% in PVC and 59% in visual association cortex.

Among our control subjects, no age-dependent differences in VIR were noted, a finding consistent with reports by Dastur et al. (19) and Gur et al. (20). Dastur et al. found no difference in brain \( O_2 \) metabolism and blood flow in healthy young (mean age, 21 years) subjects or elderly (mean age, 71 years) subjects. In contrast, in another group of elderly subjects (mean age, 73 years), even slight atherosclerotic alteration of the brain vessels significantly lowered blood flow. They concluded that elderly people with no cerebrovascular alteration have the same capacity for blood flow regulation as young people.

In the control subjects, we found no significant difference in VIR between the left and right PCA, except for the reaction to the colored slide, which increased blood flow velocity more in the right PCA than in the left PCA. These results are in contrast to a TCD study of Harders et al. (21) who found a significantly higher VIR to all visual stimuli on the right side when projecting to visual hemifields. We did not project the visual stimuli to the visual hemifields. We did not project the visual stimuli to the nonaffected side.

Visual imagery did not produce an increase in PCA flow velocity. On the contrary, in many subjects blood flow velocity slightly decreased, probably because of an activation of neighboring cortical areas during the task. With single photon emission computed tomographic studies, Goldenberg et al. (10–13) identified a region in the left inferior temporal–occipital cortex that was activated specifically during visual imagery tasks. An explanation for the failure to detect a flow velocity increase in the PCA during the imagery task could be that visual imagery, as a modality of specific memory tasks, mainly activates temporotemporal structures that are supplied by the temporal branches of the MCA.

Urban et al. (7) showed that the reduced VIR in response to photic stimulation in patients with occipital lobe infarction depends on the extent of damaged brain tissue. In support of their findings, in this study we found that patients with PCA territory infarctions had normal baseline flow velocities and reduced VIR values. The residual VIR was significantly less in patients with complete homonymous hemianopsia than in patients with quadrantanopsia. Whereas Urban et al. (7) stimulated subjects with flashed light only, we stimulated patients with complex stimuli and could show that patients with quadrantanopsia patients had normal VIR after complex scene stimulation, indicating a sparing of association cortex in these patients. We conclude that there is a direct correlation between VIR and the extent of nonaffected PVC in patients with circumscribed PCA territory infarctions. Furthermore, we are the first to investigate \( CO_2 \)-induced vasomotor reactivity in the PCA, its relation to the extent of PCA territory infarction, and its relation to VIR. This question is of special interest because \( CO_2 \) and visual stimulation involve different mechanisms: \( CO_2 \) leads to dilation of the arterioles directly, whereas VIR is dependent on neuronal activation and is probably mediated metabolically by \( K^+ \), \( H^+ \) and adenosine (9). After stroke, \( CO_2 \) reactivity is reduced because of dilated arterioles in the penumbra of the ischemic lesion, especially in patients with infarction due to internal carotid artery occlusion (22). Some investigators (23,24) have shown that the \( CO_2 \) vasomotor reserve in patients with PCA territory infarctions was not reduced when inspecting the basilar artery and have thereby concluded that these infarctions were caused by embolism. This was in line with Weller et al. (25) who demonstrated no \( CO_2 \) reserve decrease in patients with cardiac embolic infarction of the middle cerebral artery. In contrast, our data show that \( CO_2 \) reactivity is reduced to a degree that corresponds to the extent of the PCA territory infarction, although PCA territory infarctions are known to be caused embolically. Until now, there are no data about

<table>
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<tr>
<th>Quadrant-anopics</th>
<th>Affected PCA</th>
<th>Nonaffected PCA</th>
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<tbody>
<tr>
<td>Baseline flow (cm/s)</td>
<td>( 33.6 \pm 8.3 )</td>
<td>( 33.6 \pm 10.2 )</td>
</tr>
<tr>
<td>Color (%)</td>
<td>( 21.9 \pm 5.7 )</td>
<td>( 21.9 \pm 5.7 )</td>
</tr>
<tr>
<td>Complex scene (%)</td>
<td>( 32.6 \pm 7.1 )</td>
<td>( 32.6 \pm 7.1 )</td>
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<tr>
<td>Visual imagery (%)</td>
<td>( 4.7 \pm 7.4 )</td>
<td>( 4.7 \pm 7.4 )</td>
</tr>
<tr>
<td>( CO_2 )-test (%)</td>
<td>( 21.3 \pm 8.2 )</td>
<td>( 21.3 \pm 8.2 )</td>
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TABLE 2. Patients with PCA territory infarctions: baseline flow (cm/s), mean percent increase in blood flow velocity (%) and standard deviations of the affected and nonaffected PCA in response to various stimuli.

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CO₂ reactivity in the PCAs of patients with PCA territory infarctions. It is interesting that our patients showed a correlation between the extent of PCA infarction and the reduction in CO₂ reactivity. We are the first to show that reduced VIR to simple and complex stimuli resulting in decreased functional activation and reduction in CO₂ reactivity in patients with PCA territory infarctions occur in parallel.

Patients with hemianopsia due to PCA territory infarction sometimes are severely impaired in coping with daily activities because of visual field deficits. In the rehabilitation of these patients, visual hemifield training using electronic devices helps to correct visual deficits to some degree (26,27). Therefore, in the assessment of the course and prognosis of acute PCA territory infarctions, it could be helpful to use TCD-VIR measurement to supplement computed tomography or magnetic resonance tomography, because it is easy to perform. Further applications to the clinical routine will be explored in follow-up studies using VIR measurements.

REFERENCES

The Many Faces of Sarcoidosis

James D. Izer, B.S., Andrew G. Lee, M.D., Ramon L. Font, M.D., and James R. Patrinely, M.D.

A 42-year-old African-American woman saw her internist in December 1996 with symptoms of binocular vertical diplopia, headache, and a bulging, painful right eye (RE). Two weeks before, she had undergone an uneventful left lower jaw root canal. Examination revealed proptosis RE and a moderate abduction deficit RE. Complete blood count, serum chemistry, thyroid function studies, antinuclear antibody, and rheumatoid factor were normal. A magnetic resonance (MR) scan of the head and orbits revealed a soft tissue density behind the right globe, involving the medial rectus muscle RE. She was diagnosed with orbital pseudotumor and treated with 60 mg oral prednisone daily. The diplopia, headache, and eye pain improved but did not resolve.

The patient was referred to the neuro-ophthalmology service in February 1997. Visual acuity was 20/20 in both eyes. The pupils were isocoric and reacted normally to light with no relative afferent pupillary defect. Hertel exophthalmometry measured 21 mm in both eyes. Motility examination showed a moderate abduction deficit RE, and there was a 10-prism diopter esotropia in primary gaze. Slit lamp examination showed conjunctival injection and an inferior corneal micropannus RE. The remainder of the ocular examination was unremarkable. An erythematous, indurated papular lesion with a central umbilication on the right malar eminence was present (Fig. 1).

A second MR scan of the orbits revealed soft tissue density within the orbital fat surrounding the globes bilaterally, with inhomogeneous enhancement after administration of gadolinium–diethylenetriaminepentaacetic acid (DTPA). Angiotensin-converting enzyme level, Lyme titer, syphilis serology results, antineutrophil cytoplasmic antibody levels, and chest radiograph were normal. A biopsy specimen obtained from the malar skin lesion showed confluent epithelioid granulomas with multinucleated giant cells and scattered lymphoplasmacytic infiltrates (Fig. 2). Small foci of fibrinoid necrosis were present. A gallium scan showed abnormal uptake in the lacrimal glands bilaterally.

Systemic sarcoidosis has many different skin manifestations. The papular form (also known as miliary sarcoidosis) has symptoms of small papules on the face, eyelids, and neck, often with lichenification and pitting. Lupus pernio displays violaceous, smooth, shiny plaques.
on the ears, forehead, nose, and digits. Erythema nodosum exhibits erythematous, warm, tender nodules up to 5 cm in diameter, usually appearing on the shins and the face. Other skin forms include hypopigmentation, psoriasiform, and ulcerative sarcoid (1). The incidence of skin involvement in sarcoidosis has been reported to be 25% (2,3) and ocular involvement occurs in 27% to 40% of patients (2-4). As many as 54% of ocular sarcoid patients have skin involvement at the time of diagnosis, usually manifested as erythema nodosum or skin plaques (5). This case is unusual because the diagnosis of sarcoid with presumed orbital involvement was made on analysis of a skin biopsy specimen despite a normal angiotensin-converting enzyme level and chest radiograph. Ophthalmologists should be aware of the dermatologic manifestations of sarcoid and the utility of skin biopsy in diagnosis.

REFERENCES

Sinus Histiocytosis With Massive Lymphadenopathy Involving the Orbit: Reversal of Compressive Optic Neuropathy After Chemotherapy

Sharon Goldberg, M.D., Panna Mahadevia, M.D., Michael Lipton, M.D., and Pearl S. Rosenbaum, M.D.

A 38-year-old woman from Antigua had compressive optic neuropathy of the right eye caused by orbital involvement with sinus histiocytosis. There was also nasal sinus involvement and massive cervical lymphadenopathy resulting in radiographic compression of the airway and carotid sheath. Because of the compressive optic neuropathy and threat to the airway and carotid perfusion, the patient underwent a 6-month chemotherapeutic regimen of cyclophosphamide, vincristine, and prednisone. After chemotherapy, the visual dysfunction resolved in correlation with diminution of the orbital mass, and marked regression of the cervical lymphadenopathy. This case demonstrates the potential efficacy of chemotherapy in the treatment of compressive optic neuropathy in cases of orbital sinus histiocytosis with massive lymphadenopathy.

Key Words: Chemotherapy—Optic neuropathy—Rosai-Dorfman disease—Sinus histiocytosis with massive lymphadenopathy.

Sinus histiocytosis with massive lymphadenopathy (SHML) is a benign pseudolymphomatous disorder defined by the characteristic histopathologic features of sinus histiocytic proliferation and lymphocytophagocytosis (1,2). Rosai-Dorfman disease (RDD) is used synonymously with SHML or is considered the preferred eponym for soft-tissue involvement by sinus histiocytosis in the absence of lymphadenopathy (3,4). Although several case reports had been published previously (5-8), Rosai and Dorfman established SHML as a well-recognized clinicopathologic entity with their description of four cases in 1969 (1) and documentation of 30 additional cases in 1972. By 1990, Foucar et al. (2) identified 423 patients with this disease. SHML has been reported worldwide, typically occurring in the first two decades of life. The age of onset may range, however, from birth to the eighth decade. Patients with extranodal SHML are generally older at the time of disease onset (40 years) (3). Overall, blacks and whites are equally affected, and there is a slight male predominance (58%).

Typically, patients are in otherwise good health and exhibit slowly progressive, painless, bilateral lymphadenopathy. Systemic manifestations variably include fever and weight loss. Anemia, neutrophilia, polyclonal hyperglobulinemia, and elevated erythrocyte sedimentation rate are the most commonly associated laboratory findings (2,3,10). The cervical lymph nodes are most often involved. Occasionally there is enlargement of the axillary, mediastinal, and inguinal chains (1,2). Extranodal sites of involvement are noted in approximately 40% of patients, with the most frequent sites being the skin, nasal cavity and paranasal sinuses, soft tissue, eyelid, orbit, and bone (2).

CASE REPORT

A 38-year-old woman from Antigua described an 8-month history of blurring of vision on the right. She denied trauma, diplopia, or eye pain. Simultaneously, she also noted a gradually enlarging, nontender mass on the right side of her neck. Two months after the onset of her visual symptoms, there was right nasal congestion and epistaxis. Review of systems was otherwise negative.

Physical examination showed a well-developed and well-nourished woman with a firm, nontender mass on the right side of her neck. Two months after the onset of her visual symptoms, there was right nasal congestion and epistaxis. Review of systems was otherwise negative.

Physical examination showed a well-developed and well-nourished woman with a firm, nontender mass posterior to the right sternocleidomastoid muscle, measuring 8 x 5 cm. On ophthalmologic examination, best corrected visual acuity measured 20/40 OD and 20/20 OS. There was 2 mm of proptosis on the right. The motility examination produced normal findings. Static visual field testing using a Humphrey perimeter revealed an inferior altitudinal defect on the right and a full visual field on the left. On color vision testing (Ishihara 15...
plates) the patient could identify 3 plates with the right eye and 15 with the left eye. There was 25% red and brightness desaturation in the right eye. Intraocular pressures by applanation tonometry were normal. The pupils were reactive to light, but the right pupil was sluggish. Slit lamp and dilated fundus examinations were unremarkable.

The results of laboratory studies showed only mild

FIG. 1. Axial computed tomogram of the head discloses proptosis of the right globe, soft tissue infiltration of the posterior portion of the right orbit extending to the apex, as well as opacification of the right ethmoid and sphenoid sinuses (A). Coronal T1-weighted magnetic resonance image (B) and axial computed tomogram (C) demonstrate massive posterior triangle and deep cervical lymphadenopathy (open arrows). Mass effect on the carotid artery (arrowheads) and airway (A) as well as compression of the right internal jugular vein (arrow) are evident.
anemia. Contrast-enhanced computed tomography (CT) of the head and neck demonstrated an enhancing mass within the posterior portion of the right orbit, extending to the apex, and infiltration and expansion of the right ethmoid sinus with bowing of its lateral wall into the orbit (Fig. 1A). Opacification of the right sphenoid sinus was also present. There was massive posterior triangle and deep cervical lymphadenopathy extending inferiorly to the level of the suprACLavicular fossa. This lesion caused compression of the right internal jugular vein, medial deviation of the right carotid artery, and mass effect on the airway (Figs. 1B, 1C).

An open exploration of the right neck mass was performed, resulting in incisional biopsy of one of the massively enlarged cervical lymph nodes. Punch biopsies of the right ethmoid sinus were also performed.

**PATHOLOGIC FINDINGS**

Histopathologic examination of the lymph node specimen showed marked distortion and obliteration of the normal sinus architecture by significant intranodal fibrosis. There was heavy cellular infiltration, in part lymphoid, of the biopsy tissue, divided into nodules or incomplete lobules by thick bands of collagen. Rare lymphoid follicles with germinal centers were noted (Fig. 2). The cellular infiltrate consisted of small, mature lymphocytes, plasma cells, Russell bodies, and histiocytes (Fig. 3). The histiocytes often formed sheets and characteristically contained a single, vesicular nucleus, small nucleolus, and abundant pale vacuolated cytoplasm. Emperipolism—that is, intracytoplasmic sequestration of apparently viable cells of hematopoietic origin—was prominent. There were numerous histiocytes containing predominantly lymphocytes as well as a few plasma cells, neutrophils, and erythrocytes. Touch preparations of the lymph node also showed prominent emperipolism (Fig. 4). The histiocytes exhibited strong cytoplasmic immunopositivity for S-100 protein and for macrophage markers (lysozyme, MAC-387; Fig. 5).

Plasma cell infiltration was most prominent in areas of fibrosis and collagenization. Congo red stain was negative for amyloid and the frozen section and cytospin immunophenotyping studies showed polyclonality, thus excluding the possibility of a plasma cell disorder with amyloid deposits.

Examination of specimens obtained in punch biopsy of the right ethmoid sinus showed heavy lymphoplasmacytic and histiocytic proliferation, without evidence of micro-organisms. A diagnosis of sinus histiocytosis with massive lymphadenopathy was made.

**CLINICAL COURSE**

Because of the optic neuropathy and airway compression, the patient underwent treatment with a 6-month course of combination chemotherapy consisting of cytotoxan, vincristine, and prednisone. Subsequent to the chemotherapy, there was marked diminution of the cervical lymphadenopathy to 1 cm × 1 cm. There was resolution of the compressive optic neuropathy. The visual acuity improved to 20/20 OD and repeat static testing revealed a full field on the right. Color vision improved so that the patient could identify 13/15 Ishihara plates OD. There was no red or brightness desaturation, and the pupils were equally reactive. Computed tomographic scan evaluation three months after the completion of chemotherapy demonstrated significant resolution of the
right orbital infiltrate (Fig. 6A) and cervical lymphadenopathy (Fig. 6B). Ethmoidal opacification persisted.

The patient remained stable when last examined 5 months after the completion of chemotherapy, after which time she was lost to follow-up.

**DISCUSSION**

Of the 423 patients reported in the 1990 registry, 36 had documented ophthalmologic involvement as follows: eyelid (5 patients), orbit (22 patients), or both (9 patients) (2). The majority of cases involving the orbit were reported in black men (2). Patients with orbital involvement often have other sites of extranodal disease, including the nasal cavity, paranasal sinuses, skin, lower respiratory tract, and liver (2), with the presence of nasal sinus or nasal mucosal involvement being the most common (2,11). Ophthalmic disease generally localizes to the peripheral orbital soft tissues rather than to the muscle cone (10,12). Eyelid involvement occurs either as an extension of orbital involvement or as an isolated ophthalmologic finding (10,13-15). Ocular involvement in the form of unilateral anterior uveitis (16), panuveitis (10), or epibulbar limbic infiltration (17) has also been reported.

The reported signs and symptoms of orbital SHML include exophthalmos (most frequent) (2,12,18), lagophthalmos, blurred vision, diplopia, conjunctival injection, dry eye, and ocular irritation (10). Major ocular morbidity relates to the sequelae of proptosis: exposure keratopathy, corneal ulceration, endophthalmitis, and ultimately, loss of the eye (10,12,13). There are rare reports of visual impairment (11); however, the precise cause of the deficit is not recorded.

Histopathologically, a cellular infiltrate of plasma cells and histiocytes is seen in orbital SHML, similar to that seen in nodal SHML. Histiocytic proliferation in cords and nests simulates the sinusoidal pattern of the lymph node. In extranodal SHML, however, fibrosis is more common (2) and lymphocytophagocytosis is less frequent (10).

The prognosis of patients with SHML correlates with the number of nodal and extranodal areas involved (2). The disease course is generally protracted but self-limiting, with eventual spontaneous regression of lymphadenopathy and extranodal disease within several months to years (9). Medical or surgical intervention is reserved for those cases in which the disease threatens life or organ function. To date, no specific treatment protocol has been established. However, chemotherapeutic (10,14,18-21) and surgical (4,10,12,22) approaches have been used to treat the disease successfully in a limited number of cases. A combination of Vinca alkaloid, alkylating agent, and corticosteroid seems to be the most effective chemotherapeutic regimen (14,19,21). An isolated report of successful resolution of disease using acyclovir has been reported (20). Although radiotherapy has decreased mass size in some patients (13), many
FIG. 6. Contrast enhanced axial computed tomography of the head (A) and neck (B) 3 months subsequent to the completion of chemotherapy. The right orbital infiltrate has largely resolved (A), and the sphenoid sinus is clear. Persistent opacification of the ethmoid sinus is seen. Marked regression of the lymphadenopathy (B, open arrows) resulted in symmetry of the airway (A), carotid arteries, and jugular veins.

Clinicians report only limited success with this treatment (9,20).

Surgical excision has most successfully been employed for disease eradication in patients with discrete and isolated masses (4,10,19,22). Despite medical or surgical intervention, occasional deaths have been reported, but few were attributed directly to SHML (2,9). The presence of immune-mediated disease (e.g., autoimmune hemolytic anemia, arthritis, severe systemic infections, glomerulonephritis, asthma, and juvenile-onset diabetes mellitus) in association with SHML is an unfavorable prognostic indicator and is associated with increased mortality (2).

The patient described in our case clinically manifested compressive optic neuropathy and compression of the airway and carotid sheath. She was therefore treated with combination chemotherapy consisting of a Vinca alkaloid (vincristine), alkylating agent (cytoxan), and corticosteroid (prednisone). As documented in other cases, our patient responded to chemotherapy with significant resolution of the lymphadenopathy and decreased orbital infiltration (14,21,23).

Of particular clinical significance in our case was the reversal of the compressive optic neuropathy after chemotherapy, correlating with the diminution of the orbital infiltrate, demonstrated by computed tomography. The potential efficacy of chemotherapy in the treatment of compressive optic neuropathy due to orbital involvement in SHML is thus illustrated.

REFERENCES


Tamoxifen Retinopathy

Andrew G. Lee, M.D.

CASE REPORT

A 64-year-old woman had bilateral visual loss. She had received a diagnosis of breast cancer in 1992 and had undergone local surgical resection, axillary lymph node dissection, and local radiotherapy with good results. She was treated with 20 mg adjuvant tamoxifen daily, and there was no evidence of recurrent or metastatic disease. She had not been exposed to canthoxanthine. In June 1997, she had painless, bilateral, progressive loss of visual acuity, with measurements of 20/25 right eye and 20/60 left eye. Ophthalmoscopy showed a cluster of yellow-white refractile crystals in the macula of each eye (Fig. 1). A few perimacular retinal hemorrhages were also noted; the patient had a long history of known diabetes and hypertension. A diagnosis of tamoxifen retinopathy was made, and the tamoxifen was discontinued. Visual acuity did not improve, and the exam has remained stable.

Tamoxifen is used in antiestrogen chemotherapy as a treatment for breast cancer. The drug may cause corneal opacity, decreased visual acuity, and crystalline retinopathy. The superficial refractile deposits may represent byproducts of axonal degeneration. In addition, retinal hemorrhages, retinal pigment epithelial changes, and cystoid macular edema may occur. It is not known whether retinal hemorrhages in this patient were related to tamoxifen retinopathy or to underlying diabetes and hypertension.

REFERENCE

Bilateral Internuclear Ophthalmoplegia Related to Chronic Toluene Abuse

Jennie Hunnewell, M.D., and Neil R. Miller, M.D.

A 36-year-old woman exhibited slurred speech, progressive ataxia, blurred vision, and oscillopsia. Examination showed dysconjugate torsional nystagmus and bilateral internuclear ophthalmoplegia (INO). Further investigation revealed evidence of chronic toluene abuse. The neurologic findings in toluene abuse and the causes of bilateral INO are discussed.

Key Words: Ataxia—Internuclear ophthalmoplegia—Nystagmus—Oscillopsia—Toluene.

Toluene is an organic solvent commonly present in glues, paints, paint thinners, and other industrial products. It is often inhaled to achieve acute euphoria and alteration in consciousness. Solvent abuse typically begins in childhood and adolescence in a population that is not cognizant of the long-term consequences. This insidiously toxic substance is cheap and widely available to people of all ages. Patients who are exposed to toluene for a prolonged period can exhibit a variety of neurologic manifestations, including ataxia, tremor, anosmia, sensorineural hearing loss, dementia, corticospinal tract dysfunction, abnormal brainstem auditory-evoked potentials, and epileptic seizures (1-4). Abnormal magnetic resonance imaging findings include generalized cerebral, cerebellar, and brainstem atrophy; atrophy of the corpus callosum; loss of gray–white matter discrimination; multifocal high signal intensity in the cerebral white matter; and hypointensity of the thalami on T2-weighted images (5,6). Toluene is highly lipophilic, with a high affinity for myelin and cell membranes; however, the exact pathophysiological mechanism for toxicity is unknown.

Neuro-ophthalmologic manifestations can also develop in patients with chronic toluene toxicity. These include pendular nystagmus, ocular flutter, opsinclonus (1–3,7), and optic neuropathy (8,9). We report what we consider to be a new manifestation of toluene toxicity, bilateral internuclear ophthalmoplegia (INO).

CASE REPORT

In February 1992, a 36-year-old woman saw an ophthalmologist and reported a 6-month history of oscillopsia and a feeling that her eyes were quivering. The patient had a 21-year history of sniffing airplane glue initially, then paint sniffing, and eventually sniffing pure toluene. Three years earlier, she had begun to experience seizures characterized by intermittent episodes of a dream-like state associated with unusual activity. During these episodes, she would rub her thigh, walk around in an unusual manner, and become unresponsive to people around her. She had no recall of anything that occurred during these periods. Her seizures were thought to be related to an episode of physical abuse at age 27 when...
she was hit in the head but did not experience loss of consciousness. The patient was treated with valproic acid for 3 years and was subsequently prescribed carbamazepine (Tegretol; Ciba Pharmaceuticals, Broomfield, CO, U.S.A.), which she had been taking for 10 months when her visual symptoms began.

The patient had undergone a complete ocular examination in June 1990, 16 months earlier, when the physician who evaluated her reported normal findings, including ocular motility. In July 1991, 7 months earlier, a neurologic examination revealed nystagmus, intention tremor, mild gait ataxia, mild dysdiadochokinesia, and generalized hyperreflexia. The patient reported that she was not abusing alcohol or drugs at that time. Magnetic resonance imaging showed mild atrophic changes of the brainstem and cerebellum. Shortly thereafter, oscillopsia developed, followed by slurred speech, and increasing difficulty walking.

On examination in February 1992, the patient's visual acuity was 20/30 OD and 20/25 OS. She had conjugate, horizontal, nystagmus that was primarily pendular but had a jerk component, with the fast phase to the right. The nystagmus was initially thought to be related to the effects of carbamazepine, which was then discontinued. However, the patient continued to have oscillopsia, and another examination revealed worsening nystagmus, which was somewhat disconjugate, with a torsional component. In addition, the patient exhibited a wide-based unsteady gait and tended to lose her balance whenever she attempted to turn around while standing in place. An electroencephalogram showed diffuse slowing, and another magnetic resonance imaging scan revealed generalized cerebral and cerebellar atrophy and diffuse atrophy of the corpus callosum. A few small focal areas of nonenhancing abnormal increased signal were present in the right putamen, left internal capsule, left frontal lobe white matter, and right side of the brainstem. A more diffuse increased signal was present in the periventricular white matter surrounding the frontal and posterior horns of the lateral ventricles. It was suspected that the patient had chronic multiple sclerosis (MS), and the physician decided to observe her at regular intervals. Approximately 15 months later, her family disclosed for the first time the patient's history of toluene abuse.

In February 1994, the patient saw an ophthalmologist with a report of persistent oscillopsia. She had no numbness, paresthesia, bowel or bladder abnormality, Uhthoff's symptom, or Lhermitte's sign. Best corrected visual acuity was 20/100 OU. The patient identified five of 10 Hardy-Rand-Rittler pseudoisochromatic plates correctly with each eye. Visual fields were full. In primary position, the patient had disconjugate, primarily pendular nystagmus. In addition, the patient had moderate bilateral limitation of adduction associated with bilaterally slowed adducting saccades and horizontal jerk nystagmus in the abducting eye, consistent with bilateral INO (Fig. 1). A third magnetic resonance imaging scan showed the previously noted changes. In addition, sev-
eral hyperintense lesions were present on both sides of thepons, some of which were in the region of themedial longitudinal fasciculi (Fig. 2). Analysis of cerebrospinal fluid obtained in a lumbar puncture showed normalconcentrations of glucose and protein, no white blood cells,noonliglionic bands, and no evidence of myelin basicprotein. A diagnosis of neurotoxicity caused by chronictoluene abuse was made. When last evaluated in 1995,thepatient had severe dysarthria, ataxia, and tremor. Thebilateral INO and nystagmus were still present.

**DISCUSSION**

Unilateral and bilateral INO are often caused by ischemiainflammatory disease, particularly MS; however,a variety of other causes can produce INO (Table 1) (10).In particular, a variety of substances, including phenothiazines (11), tricyclic antidepressants (12-14), narcotics (15,16), barbiturates (17), propranolol (18), and lithium (19) can cause neurotoxicity that includes bilateral INO. In our patient, MS was considered the mostlikely cause of the patient’s neurologic disorder, and thepatient underwent neuroimaging studies and a lumbarpuncture in an attempt to confirm this diagnosis. Whentheses studies failed to confirm a diagnosis of MS, alternativecauses were considered.

Our case indicates that toluene should be added to thelist of causes of an INO and that chronic toluene abuse shouldbe considered in any patient who has pendularnystagmus associated with bilateral INO, particularlywhen neuroimaging studies, lumbar puncture, evokedpotentials, serologic studies, or a combination of these diagnostic techniques failed to document the presenceof any of the more common causes of the disorder, such asMS or vasculitis. This is especially important because,although the neurotoxicity of toluene can produce a clinicapicture similar to that of MS (5), patients who abuse tolue nemay experience improvement in neurologic andocular manifestations with abstinence from the substance(1), whereas continued abuse can result in a progressive decline in neurologic function.

**TABLE 1. Etiology of bilateral internuclear ophthalmoplegia**

<table>
<thead>
<tr>
<th>1. Demyelination</th>
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<tbody>
<tr>
<td>a. Multiple sclerosis</td>
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<tr>
<td>b. Postirradiation demyelination</td>
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<tr>
<td>2. Brainstem infarction</td>
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<tr>
<td>a. Hypertension</td>
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<tr>
<td>b. Diabetes mellitus</td>
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<td>c. Vasculitides (e.g., systemic lupus erythematosus, temporal arteritis)</td>
</tr>
<tr>
<td>d. Complications of arteriography</td>
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<tr>
<td>3. Brainstem hemorrhage</td>
</tr>
<tr>
<td>4. Brainstem and 4th ventricular tumors</td>
</tr>
<tr>
<td>5. Mesencephalic cleft</td>
</tr>
<tr>
<td>6. Chiari malformation, and associated hydrocephalus and syringobulbia</td>
</tr>
<tr>
<td>7. Infection, including bacterial, viral, spirochetal, and other forms of meningoencephalitis</td>
</tr>
<tr>
<td>8. Hydrocephalus</td>
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<tr>
<td>9. Subdural hematoma</td>
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<tr>
<td>10. Supratentorial arteriovenous malformation</td>
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<tr>
<td>11. Nutritional disorders</td>
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<tr>
<td>a. Wernicke encephalopathy</td>
</tr>
<tr>
<td>b. Pernicious anemia</td>
</tr>
<tr>
<td>12. Metabolic disorders</td>
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<tr>
<td>a. Hepatic encephalopathy</td>
</tr>
<tr>
<td>b. Maple syrup urine disease</td>
</tr>
<tr>
<td>c. Abetalipoproteinemia</td>
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<tr>
<td>d. Fabry disease</td>
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<tr>
<td>13. Drug intoxications</td>
</tr>
<tr>
<td>a. Phenothiazines</td>
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<td>b. Tricyclic antidepressants</td>
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<tr>
<td>c. Narcotics</td>
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<tr>
<td>d. Propranolol</td>
</tr>
<tr>
<td>e. Lithium</td>
</tr>
<tr>
<td>f. Barbiturates</td>
</tr>
<tr>
<td>g. Toluene</td>
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<tr>
<td>14. Cancer</td>
</tr>
<tr>
<td>a. Direct effect (e.g., brainstem infiltration)</td>
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<tr>
<td>b. Remote (paraneoplastic) effect</td>
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<tr>
<td>15. Injury</td>
</tr>
<tr>
<td>a. Blunt head trauma</td>
</tr>
<tr>
<td>b. Cervical hyperextension</td>
</tr>
<tr>
<td>c. Neck manipulation (e.g., chiropractic)</td>
</tr>
<tr>
<td>16. Degenerative conditions (e.g., progressive supranuclear palsy)</td>
</tr>
<tr>
<td>17. Pseudobilateral internuclear ophthalmoplegia of nystagmic grade and mycotic dysophoria</td>
</tr>
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</table>


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Mobius Syndrome With Oculomotor Nerve Paralysis Without Abducens Paralysis

Dan B. Tran, M.D., Martin C. Wilson, M.D., Catherine A. Fox, M.S., OTR/L, Robert Clancy, M.D., James W. Teener, M.D., Jeffrey A. Golden, M.D., and Grant T. Liu, M.D.

Mobius syndrome is typified by bilateral facial nerve palsies, usually with abducens palsies. We examined an infant with Mobius syndrome who had bifacial weakness and third nerve palsies, but intact abduction of both eyes. Lower cranial nerve involvement, leading to respiratory, swallowing, and cardiac difficulties, was also present. Pathologic examination of the brainstem showed absent or hypoplastic third, seventh, tenth, and twelfth nerve nuclei. The fourth, fifth, sixth, and eighth nerve nuclei were intact. In Mobius syndrome with ocular motor palsies, rarely the sixth nerve may be spared.

Mobius syndrome was classified by Mobius in 1888 [1]. The main feature is congenital bilateral facial nerve palsies, often with abducens palsies. The clinical features were later expanded to include multiple cranial nerve defects [2], craniofacial malformations with limb anomalies [3], and somatocutaneous dysmorphic features [4].

We report a case of congenital bilateral facial nerve and pupil-sparing oculomotor nerve palsies without abducens palsies.

CASE REPORT

The patient was delivered via Caesarean section at 42 weeks of gestational age. The mother was a G4P2 with negative syphilis, hepatitis, and HIV serologies. The baby girl was noted to have poor respiratory effort and was intubated shortly after birth. Her Apgar scores were 2 at 1 minute, 3 at 5 minutes, and 6 at 10 minutes. Her subsequent hospital course was significant for hypotensive episodes.

The patient was noted to have poor eye opening, and neuro-ophthalmic evaluation showed bilateral ptosis with no facial movements on either side. She had a large angle exotropia with adduction, elevation, and depression deficits (Fig. 1). Her pupils were reactive to light without an afferent pupillary defect. Her anterior segment and fundus exams were normal without coloboma. Electromyographic studies (EMG) were performed showing markedly reduced or absent innervation of facial muscles. A few motor units were detected in lower facial muscles, but no voluntary EMG activity was identified in upper facial muscles. The results of a Edrophonium (Tensilon) test were negative, and her electroencephalogram results were normal. Magnetic resonance imaging prior to discharge showed a right frontal subdural hematoma, thin corpus callosum, and normal optic chiasm, pons, and midbrain. Chromosomal analysis was unremarkable.

In the neonatal intensive care unit, the patient had poor respiratory effort associated with a large floppy epiglottis and normal cord mobility with multiple failed attempts at extubation; she subsequently underwent successful tracheostomy. A swallowing study showed no pharyngeal motility, with subglottic aspiration, and a G-tube was placed without complication.

On subsequent exam at the age of 6 months, the patient continued to have complete bilateral ptosis and no facial strength bilaterally. She preferred her right eye and the left eye was markedly exotropic. She continued to have bilateral adduction, supraduction, and infraduction deficits. Her pupils were 3 mm and reactive. She had no intorsion of either eye on attempted downgaze, but this part of the examination was difficult. Alternate patching of her eyes was recommended. She had been noted to have several episodes of bradycardia throughout the day with episodes of apnea at night.

At age 2 years, the patient died unexpectedly in her sleep, and an autopsy was performed. The brain, and the brainstem in particular, showed no gross abnormalities. Histologic section from the cerebral hemispheres, basal ganglia, thalamus, and cerebellum were unremarkable. Sections of the brainstem showed cranial nerve nuclei four, five, six (Fig. 2A), and eight to be unremarkable. In contrast, there was a relative paucity of cells in the third nerve nucleus, particularly in the dorsal lateral regions. A
FIG. 1. Photograph depicting infant with bifacial paralisis and ptosis. The eyes are exotropic, and the pupils are small and reactive to light.

few reactive astrocytes were seen in the third nerve nucleus, a finding confirmed with immunohistochemistry using an antibody to glial fibrillary acid protein (data not shown). The seventh nerve nucleus was remarkable for a nearly complete absence of neurons with no evidence of a glial reaction (Fig. 2B). These changes are indicative of a primary failure of the nucleus to form or possibly of very early embryonic injury. The twelfth nerve nucleus showed similar findings to those seen in the seventh nerve nucleus. The dorsal motor nucleus of the tenth nerve showed neuronal loss and reactive gliosis similar to that seen in the third nerve nucleus. No other pathologic changes were seen in the midbrain or brainstem.

DISCUSSION

In addition to congenital facial diplegia, abducens nerve palsy is the feature most commonly associated with Möbius syndrome, occurring in 82% of the cases in the series reported by Henderson (2). In addition, total external ophthalmoplegia occurred in 25% of the cases, oculomotor palsy in 21%, and bilateral ptosis in 10%. Our patient had bilateral pupil-sparing oculomotor and facial nerve palsies. Clinically, abducens nerve function was normal. The facial nerve paralysis was confirmed by EMG studies. Pathologic examination confirmed absence or hypoplasia of the third, seventh, tenth, and twelfth nerves, but preservation of the fourth, fifth, sixth, and eighth nerves.

We have found only one other case report in the English language literature of Möbius syndrome with oculomotor and facial nerve palsies without abducens palsies. This patient also had bilateral disc colobomas (3). According to this report (3), the EMG studies were refused. They also mentioned that there was only one other case of oculomotor paralysis and facial nerve palsy without abducens palsies diagnosed as Möbius syndrome in the German literature (6).

The etiology of Möbius syndrome remains unclear but is probably multifactorial. The major theories regarding pathogenesis include primary brainstem nuclear hypoplasia, secondary brainstem nuclear degeneration, brainstem atrophy secondary to peripheral neuromuscular defect, and vascular insufficiency prior to the sixth week of gestation affecting certain brainstem structures (7,8). A cluster of familial cases challenge these theories and continue to suggest genetic predisposition (9). Neuropathologic studies (10,11) have shown that brain-stem atrophy and multiple brain-stem mineralized necrotic foci can be associated with Möbius syndrome. These studies support the hypothesis that Möbius syndrome in some patients could be the result of intrauterine asphyxia (11). Radiologic abnormalities of the brain-stem in Möbius syndrome have been reported including brain-stem hypoplasia and calcification (7).

Towfighi et al. (10) classified the neuropathologic findings in 15 autopsy cases cited in the literature into four groups. The first three groups support the anterograde theory of dysmorphogenesis in Möbius syndrome with primary developmental lesions in the cranial nerve nuclei causing secondary damage to the peripheral musculature. Sudarshan and Goldie (12) proposed that the fourth group, consisting of patients with myopathy, should be classified in a separate category because these cases have clinical features similar to congenital muscular dystrophy.

FIG. 2. Photomicrographs of the sixth and seventh nerve nuclei. (A) The sixth nerve nucleus shows a normal population of large neurons. (B) The seventh nerve nucleus shows a subtotal depletion of neurons without secondary reactive changes. The arrows point to remaining large neurons. Several smaller neurons are also seen in the background. The pathologic findings were the same on both sides of the brainstem. (A and B; Kluver stain, 200x)
lar dystrophy or congenital myopathies. No lesions were found in the brainstem or cranial nerves of this group.

The pathologic findings in our patient are consistent with two possible mechanisms, although both are highly conjectural. The absence of neurons without gliosis in some locations might have resulted from an abnormality in the genetic programming for development of those cranial nerve nuclei. However, nuclei that showed a reduced number of neurons with gliosis suggest these nuclei were the target of some secondary destructive process. With either mechanism, it is unclear why some nuclei were selectively spared.

In conclusion, this patient with pathologic confirmation expands the boundaries on the pattern of cranial nerve involvement in Möbius syndrome. This syndrome is probably a part of the spectrum of congenital neuromuscular disorders, often with unknown etiology.

REFERENCES
Patient With Kearns–Sayre Syndrome Exhibiting Abnormal Magnetic Resonance Image of the Brain

Yuko Kamata, M.D., Yukihiko Mashima, M.D., Masako Yokoyama, M.D., Kortaro Tanaka, M.D., Yu-ichi Goto, M.D., and Yoshihisa Oguchi, M.D.

A 33-year-old Japanese man had Kearns–Sayre syndrome (KSS), which consists of the triad of external ophthalmoplegia, heart block, and "salt-and-pepper" retinopathy. The other systemic manifestations included sensorineural hearing loss, slight generalized muscle weakness, cerebellar ataxia, and elevated levels of cerebrospinal fluid protein. He exhibited a heteroplasmic mitochondrial DNA deletion of approximately 9 kb between the cytochrome c oxidase subunit 1 and cytochrome b genes. In the authors' experience, this deletion is one of the longest to be observed in such patients. His fundi were characterized bilaterally by white flecks in the inner layers of retina at the midperiphery. Visual evoked potentials showed delayed latency in the P100 component. The tibial somatosensory evoked potential revealed a marked prolongation of interpeak latency between the N20 and P40 components. Brain magnetic resonance images revealed high-intensity foci in several regions on T2-weighted images. Electrophysiological and magnetic resonance imaging findings suggested an involvement of the white matter of the central nervous system in this patient that was not reflected in the clinical findings.

Key words: Brain magnetic resonance imaging—Kearns–Sayre syndrome—Flecked retina—mtDNA deletion—Somatosensory evoked potential—Visual evoked potential.

Kearns–Sayre syndrome (KSS) is a progressive, multisystemic disorder that is characterized by the triad of progressive external ophthalmoplegia, atypical pigmented degeneration of the retina, and cardiac conduction defects (1–3). More recently, patients with KSS have been reported to show such other clinical manifestations as mental retardation, cerebellar dysfunction, sensorineural hearing loss, concentration of protein higher than 100 mg/dl in cerebrospinal fluid (CSF), various endocrine system dysfunctions, and elevated serum or CSF levels of lactate and pyruvate (3–5). This syndrome is a sporadic condition, with onset before 15 to 20 years of age. Because mitochondrial abnormalities such as ragged red fibers (6) and deficiencies in respiratory chain enzymes have been detected in examination of muscle biopsy specimens, it is considered to be a mitochondrial disease (7,8). Patients with KSS typically show large-scale heteroplasmic deletions of mitochondrial DNA (mtDNA) (4,9,10).

We report the clinical features of a Japanese man with KSS who exhibited a deletion of 8957 base pairs (bp) spanning between the cytochrome c oxidase subunit 1 (CO1) and cytochrome b (Cyt b) genes, and sparing two replication origins. The size of the deletion was the largest found in 65 Japanese patients with chronic progressive external ophthalmoplegia (CPEO) or KSS (4 and Goto et al., 1995, unpublished data).

CASE REPORT

After a traffic accident, a 33-year-old Japanese man was transferred to the Keio University Hospital on August 12, 1993. Routine radiographs of the chest and skull revealed no abnormalities, but an electrocardiogram showed complete right bundle branch block and left anterior hemiblock. The patient also evidenced external ophthalmoplegia, ptosis, and hearing loss, all of which were unrelated to the accident. His medical history showed development of bilateral blepharoptosis, abnormal eye movements, and hearing loss at age 10. An operation to correct bilateral ptosis had been performed when he was 11. There was no family history of metabolic, neurologic, or neuromuscular disorders. This unusual patient was therefore admitted to our hospital for detailed evaluation.

Ophthalmologic Findings

Best-corrected visual acuity was 20/25 in the right eye and 20/60 in the left eye, and refraction was +0.5 - 2.0 x 180 in the right eye and +1.0 - 7.0 x 180 in the left eye; visual acuity was 20/40 with correction by contact lens in the left eye. The pupils reacted promptly to light. Bilateral blepharoptosis and incomplete external ophthalmoplegia were present. Intracocular pressure was 12 mm Hg in each eye. The anterior segment and optic
FIG. 1. A: Photograph of fundus in the right eye shows salt-and-pepper retinopathy with glistening whitish deposits in the superficial and deep intraretinal layers of midperipheral retina with a circinate pattern. B: Fluorescein angiogram in the right eye shows a salt-and-pepper pattern of irregular atrophy of the retinal pigment epithelium with diffuse hyperfluorescence and hypofluorescence.

media were normal in each eye, but the presence of marked corneal astigmatism (approximately 7 D) caused anisometropic amblyopia in the left eye. Examination by specular microscopy showed enlarged endothelial cells with polymegathism and pleomorphism in both eyes.

Ophthalmoscopic examination revealed bilateral conuslike atrophy around the optic discs and atypical pigmentary retinopathy consisting of mottled pigmentation, so-called salt-and-pepper retinopathy (11) (Fig. 1A). Optic discs were normal in color. There was no bone spicule pigmentation, as is typically seen in retinitis pigmentosa. Tiny glistening deposits were observed in the superficial and deep intraretinal layers of the midperipheral retina, mainly in the temporal retina, with a circinate pattern present in both eyes. A fluorescein angiogram showed a hypofluorescent ring around the optic disc and a salt-and-pepper pattern of irregular atrophy of the retinal pigment epithelium with diffuse hyperfluorescence and hypofluorescence (Fig. 1B). The white flecks corresponded to mottled hyperfluorescence without dye leakage or nonfluorescence. A 20-J single-flash electroretinogram (ERG) performed after 30 minutes of dark adaptation showed a slight reduction in b-wave amplitude, with attenuated oscillatory potentials. The amplitude of a 30-Hz flicker ERG was slightly reduced in both eyes (Fig. 2). Visual evoked potentials (VEPs) to pattern and flash stimulation showed delayed latency (Fig. 3).

Neurologic Evaluation

Physical examination showed that the patient was 160 cm tall and weighed 50 kg. He exhibited neurogenic hearing loss, slight generalized muscle weakness, and cerebellar ataxia. There was no evidence of mental retardation or of abnormal reflexes, and muscle tone was normal. Results of laboratory studies showed a serum creatine kinase level of 70 IU/l (normal, 67-210 IU/l); aldolase, 3 IU/l (normal, 2-5 IU/l); lactate, 9.2 mg/dl (normal, 3.3-14.3 mg/dl); and pyruvate, 0.85 mg/dl (normal, 0.3-0.94 mg/dl). An echocardiogram showed no abnormalities. An electroencephalogram showed slowing of background activity without paroxysmal discharge. An audiogram revealed bilateral sensorineural hearing loss. The results of needle electromyographic and peripheral nerve conduction studies were within normal limits. Short somatosensory evoked potentials (SSEP) after stimulation of the tibial nerve showed normal latency of the N20 component but delayed latency of the P40 component (Fig. 4). Interpeak latency between the P40 and N20 components was markedly prolonged, 31.0 msec in stimulation of the right limb and 31.4 msec in the left limb (normal, 12-22 msec in 30s). A lumbar puncture yielded xanthochromic CSF that showed concentrations of 132 mg/dl protein (normal, 15-45 mg/dl), 11 mg/dl lactate, 0.65 mg/dl pyruvate, and 14.3 mg/dl Ig (immunoglobulin) G (normal, <5 mg/dl).

A computed tomographic scan of the brain showed focal low-density lesions in the white matter and slight atrophy. A T2-weighted magnetic resonance image (MRI) of the brain showed symmetrical high-intensity lesions in the white matter, globus pallidus, internal capsule, midbrain, and left cerebellar hemisphere (Fig. 5).

FIG. 2. A 20-J single-flash electroretinogram (A) shows a slight reduction in b-wave amplitude. Oscillatory potentials (B) are slightly attenuated. The amplitude of a 30-Hz flicker electroretinogram (C) is slightly reduced.
There was no gadolinium enhancement in these lesions. These lesions were consistently observed in the brain MRI during a 3-year period of follow-up.

**Muscle Pathology and mtDNA Analysis**

A biopsy was performed in the right brachial biceps muscle, and cryostat sections were stained with hematoxylin and eosin, Gomori's trichrome stain, and a set of oxidative enzymes, including succinate dehydrogenase and cytochrome c oxidase. With Gomori's trichrome staining, approximately 1% of fibers showed an intense red band in the perimysium that was consistent with ragged red fibers. Cytochrome c oxidase activity was deficient in the ragged red fibers and the normal-appearing fibers on Gomori's trichrome stain, indicating a focal deficiency of cytochrome c oxidase.

MtDNA was extracted from the muscle specimen (4), and the deletion junction was localized, as previously described (12). Sequencing analysis revealed 8-bp direct repeats of TACTTCTC located in the boundaries of the deletion between the COI and Cyt b genes (Fig. 6A). The deletion segment spanned 8,957 bp from nucleotide position 6,484 to 15,440. Evidence of heteroplasmy was found, and the mutant constituted of 25% of total mtDNA (Fig. 6B).

**DISCUSSION**

MtDNA rearrangements are known to cause three phenotypes of mitochondrial disease: diabetes and deafness, ocular myopathy, and Pearson's syndrome (13–15). Patients with diabetes and deafness often show maternal inheritance of the disorder. However, patients with ocular myopathy or Pearson's syndrome are generally isolated cases that result from new mutations. Among the mtDNA rearrangement syndromes, CPEO is a milder form, whereas KSS is a severe form that involves multisystem failure. Our patient had a heteroplasmic mitochondrial DNA deletion of approximately 9 kb between the COI and Cyt b genes. There is reportedly no association between the size, site, or populations of deleted mtDNA and respiratory chain enzyme activities in muscles from patients with CPEO or KSS (4).

In addition to the clinical triad of KSS, our patient exhibited salt-and-pepper retinopathy with white flecks and lesions in the white matter of the brain that were confirmed by a marked delay in SSEPs and VEPs, and high-intensity areas observed on a T2-weighted brain MRI. A flecked retina is a rare manifestation of KSS. White spots or flecks in the retina have been described in only a few patients with CPEO or KSS (16–18). Retinal flecks may occur in association with systemic diseases such as primary hyperoxaluria (19), cystinosis (20), Sjögren–Larsson syndrome (21) and ring 17 chromosome (22). Of 61 patients with mitochondrial myopathy, 22 showed pigmentary retinopathy (23). Most of the patients had a salt-and-pepper type of retina, with none showing a flecked retina. Fluorescein angiograms and ERGs in our patient revealed a more marked degeneration of the retinal pigment epithelium than of the outer retina. Oscillatory potentials, which are generated more proximally than the a- and b-waves, probably by bipolar cells (24), also showed a deterioration. Electroretinogram findings resembled those in the early stage of diabetic retinopathy (25), suggesting the presence of hypoxia of the inner retina. MtDNA defects may involve mainly the neuronal retinal cells in the inner retina and retinal pigment epithelium. However, the association between the white flecks in the retina and the mtDNA deletion in this patient is unclear.

Abnormal VEPs and SSEPs have been reported in patients with mitochondrial myopathy, CPEO, or KSS (26–30). Simultaneous recordings of the pattern ERG and the pattern VEPs in patients with mitochondrial myopathy have suggested that central nervous system involvement is predominantly axonal (29). Our patient with KSS showed delayed latency in both the flash and
FIG. 5. Brain T2-weighted magnetic resonance images. A: symmetrical high-intensity lesions in the white matter (black arrow); B: symmetrical high-intensity lesions in the internal capsule (white arrow); C: symmetrical high-intensity lesions in the midbrain (black arrow); D: high-intensity lesion in the left cerebellar hemisphere (black arrow).

pattern VEPs, which may suggest the presence of lesions of the visual pathway. The patient also showed prolonged N20 to P40 interpeak times in a tibial SSEP. Previous studies of prolonged N20 to P40 conduction indicate that central somatosensory pathways are involved between the lumbar posterior column and the cerebral cortex (30). The finding of a normal N20 conduction in the present case indicates that the peripheral somatosensory nerves are not involved.

Magnetic resonance imaging may not have been feasible in most of the other studies in patients with KSS, because they may have had metallic pacemakers. Some reports of KSS patients have described areas of high intensity in the white matter of the cerebrum, cerebellum, and brainstem on T2-weighted sequences (31–34). These lesions are consistent with the clinical findings of respiratory arrest, ataxia, and pendular nystagmus associated with KSS (14). However, it is not known why the patients with large mtDNA deletions would show lesions of the white matter on MRI. The MRI of the brain in the
present case showed symmetrical, delineated, high-intensity foci in the white matter which were consistently observed on 72-weighted images during a 3-year period of observation. Examination of the CSF did not reveal any possible causes such as demyelination or inflammation. Abnormal metabolism in the deleted mitochondria may be involved in the formation of lesions of the white matter. Findings of MRI, VEP, and SSEP in our patient suggested an involvement of the central nervous system, despite the absence of relevant clinical signs.

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Proptosis With Acute Oculomotor and Abducens Nerve Palsies

Daniel M. Jacobson, M.D.

Objective: To determine whether orbital axial proptosis occurs in the affected eye of patients with acute oculomotor or abducens nerve palsy.

Materials and Methods: In this prospective, cross-sectional survey, the Hertel instrument was used to measure the amount of axial proptosis in 26 consecutive patients with complete or severe acute oculomotor nerve palsy and 27 consecutive patients with complete or severe acute abducens nerve palsy. The Mann-Whitney test was used to compare the amount of relative proptosis of the affected eye in the patient groups with that of 40 control subjects. The absolute amount of the interocular difference in axial proptosis of the normal eyes was used to determine control values. The proportion of patients and control subjects with relative proptosis greater than 1 mm was compared using Fisher's exact test.

Results: There was no significant difference in the degree of relative proptosis of the affected eye of patients with oculomotor nerve palsy or abducens nerve palsy as compared with the control eyes. Likewise, there was no significant difference in the proportion of patients with relative proptosis greater than 1 mm in either the oculomotor nerve palsy group or the abducens nerve palsy group as compared with the control group.

Conclusions: Acute oculomotor or abducens nerve palsy does not produce any significant amount of orbital axial proptosis in the affected eye, at least as measured clinically using the Hertel instrument. Acute neurogenic ophthalmoplegia rarely causes relative proptosis greater than 1 mm.

Key words: Proptosis—Orbit—Oculomotor nerve—Abducens nerve.

Axial orbital proptosis is an important sign that may reflect an intraorbital lesion in a patient with ophthalmoplegia. However, one might expect that an acute injury producing neurogenic ophthalmoplegia from an ocular motor nerve palsy could also cause some degree of relative proptosis of the affected eye due to hypotonia of the denervated extraocular muscles. Historical and modern reference textbooks contain anecdotal observations of the association between acute ocular motor nerve palsy and proptosis. For example, Kestenbaum (1) stated that the eye becomes slightly exophthalmic if several recti are paretic. Walsh (2) mentioned that in some cases of third nerve paralysis there is a definite degree of exophthalmos. Further, he indicated that he had observed as much as 3 mm of exophthalmos associated with such a process (2). Glaser (3), however, stated that there is little evidence to support the concept that oculomotor nerve paralysis causes detectable proptosis. I am not aware of any study that has formally evaluated whether proptosis occurs with ocular motor nerve palsies. The purpose of this investigation, therefore, was to determine whether axial orbital proptosis occurs in patients with acute oculomotor or abducens nerve palsies.

METHODS

The research proposal that this study was based on was reviewed by the expedited review process of the Institutional Review Board (IRB) of the Marshfield Clinic and was determined to be exempt from IRB regulation. Oral consent was obtained from each participant.

The degree of axial orbital proptosis was prospectively measured in two patient populations; the first group consisted of patients with complete or severe acute oculomotor and abducens nerve palsies, and the second group was a control group of healthy subjects. Acute was defined as a time interval of less than 2 weeks from onset of symptoms to evaluation. Severe ocular motor deficit was defined as an ophthalmoplegia that limited oculaructions by at least 75% of normal, using a previously established standardized ophthalmoplegia grading scheme for oculomotor (4) and abducens (5) nerve palsies.

The patients consisted of consecutive ambulatory individuals attending an outpatient, referral-based neuro-ophthalmology clinic. None of the patients had experienced orbital trauma or had other signs of orbital disease. The control subjects consisted of staff of the Marshfield Clinic who were selected solely on the basis of availability. None of the control subjects had symptoms of orbital disease or known disorders affecting the orbit.

Proptosis was measured using the Hertel instrument (Marco Products, Jacksonville, Florida) and a technique suggested by Rootman (6). While measuring protrusion of a subject's right eye, the examiner closed his left eye and asked the individual to look at his open right eye. Similarly, the subject was asked to look at the examiner's open left eye as he measured protrusion of their left eye. Measurements were determined at least twice for each
eye until a consistent and reproducible reading, estimated to the nearest 0.5 mm, was established. Relative proptosis of the affected eye in patients was defined as the axial measurement of the affected eye subtracted from the axial measurement of the unaffected eye. A positive value indicated that the affected eye protruded more than the unaffected eye. By convention, relative proptosis of the control subjects was determined by subtracting the axial measurement of the left eye from that of the right eye. A positive value indicated that the right eye protruded more than the left eye, whereas a negative value indicated that the left eye protruded more than the right eye.

The assigned etiology of the ophthalmoplegia was determined retrospectively by reviewing the medical records of each of the patients after all had been enrolled. The specific category of injury of the affected oculomotor nerve was determined after considering the patient’s history upon admittance, associated neurologic symptoms and medical conditions, results of laboratory and neuroimaging procedures if performed, and the natural history of the deficit.

Exophthalmometry measurements were entered into a computerized database and statistical analysis system (Graphpad Prism, San Diego, California). The Mann-Whitney test (two-tailed) was used to compare whether the degree of relative proptosis of the affected eye differed between the groups of patients with complete and severe ophthalmoplegia. Then, the Mann-Whitney test was used to compare the degree of relative proptosis of the affected eye in patients with oculomotor nerve palsy (P = 0.71) or abducens nerve palsy (P = 0.35) compared with the absolute value of relative proptosis in the control eyes. Only 4 of 26 (15%) patients with third nerve palsy and 3 of 27 (11%) patients with abducens nerve palsy had relative proptosis of their affected eye greater than 1 mm. Only 1 of 26 (4%) patients with third nerve palsy and 1 of 27 (4%) patients with abducens nerve palsy had relative proptosis of the affected eye of 2 mm or more. There was no significant difference in the degree of relative proptosis of the affected eye in patients with oculomotor nerve palsy who had complete or severe ophthalmoplegia (P = 0.72). Likewise, there was no significant difference in the degree of relative proptosis between the patients with abducens nerve palsy who had complete or severe ophthalmoplegia (P = 0.26). Accordingly, patients with complete and severe ophthalmoplegia were combined for all subsequent analyses.

The control subjects consisted of 40 healthy individuals, including 24 women and 16 men, ranging in age from 22 years to 78 years (mean, 39 years). The amount of relative proptosis in this population ranged from −1.0 mm to 1.5 mm (median, 0 mm) (Fig. 1). The average absolute value of relative proptosis was 0.38 mm (standard deviation, 0.42 mm).

The degree of relative proptosis of the affected eye in patients with oculomotor nerve palsy ranged from −1.0 mm to 2.0 mm (median, 0.5 mm), whereas the degree of relative proptosis of the affected eye in patients with abducens nerve palsy ranged from −1.0 mm to 2.5 mm (median, 0 mm) (Fig. 2). There was no significant difference in the amount of relative proptosis of the affected eye in patients with oculomotor nerve palsy (P = 0.71) or abducens nerve palsy (P = 0.35) compared with the absolute value of relative proptosis in the control eyes.


e-defined in the text as 75% limitation of ocular ductions.

### RESULTS

The study population included 26 patients with oculomotor nerve palsy and 27 patients with abducens nerve palsy. Their main demographic and clinical characteristics are summarized in Table 1. None of the patients with oculomotor nerve palsy had isolated deficits referable to the superior or inferior division. There was no significant difference in the degree of relative proptosis between the patients with oculomotor nerve palsy who had complete or severe ophthalmoplegia (P = 0.72). Likewise, there was no significant difference in the degree of relative proptosis between the patients with abducens nerve palsy who had complete or severe ophthalmoplegia (P = 0.26).

The control subjects consisted of 40 healthy individuals, including 24 women and 16 men, ranging in age from 22 years to 78 years (mean, 39 years). The amount of relative proptosis in this population ranged from −1.0 mm to 1.5 mm (median, 0 mm) (Fig. 1). The average absolute value of relative proptosis was 0.38 mm (standard deviation, 0.42 mm).

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Only 4 of 26 (15%) patients with third nerve palsy and 3 of 27 (11%) patients with abducens nerve palsy had relative proptosis of their affected eye greater than 1 mm. Only 1 of 26 (4%) patients with third nerve palsy and 1 of 27 (4%) patients with abducens nerve palsy had relative proptosis of the affected eye of 2 mm or more. There was no significant difference in the proportion of patients with either oculomotor nerve palsy (P = 0.97) or abducens nerve palsy (P = 0.29) who had relative proptosis greater than 1 mm in their affected eye as compared with the proportion of control subjects with an absolute value of relative proptosis greater than 1 mm.

### TABLE 1. Demographic and clinical features of 26 patients with acute oculomotor nerve palsy and 27 patients with acute abducens nerve palsy

<table>
<thead>
<tr>
<th></th>
<th>Oculomotor Nerve Palsy</th>
<th>Abducens Nerve Palsy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age range (mean), years</strong></td>
<td>31–86 (68)</td>
<td>40–91 (70)</td>
</tr>
<tr>
<td><strong>No. women, men</strong></td>
<td>11, 15</td>
<td>10, 17</td>
</tr>
<tr>
<td><strong>No. right, left eye affected</strong></td>
<td>14, 12</td>
<td>13, 12</td>
</tr>
<tr>
<td><strong>Etiology, no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemia</td>
<td>24 (92)</td>
<td>23 (85)</td>
</tr>
<tr>
<td>Compression</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Infiltration</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Brainstem stroke</td>
<td>0</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Undetermined</td>
<td>0</td>
<td>3 (11)</td>
</tr>
<tr>
<td><strong>Degree of ophthalmoplegia, no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>15 (50)</td>
<td>11 (41)</td>
</tr>
<tr>
<td>Severe*</td>
<td>13 (50)</td>
<td>16 (59)</td>
</tr>
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* Defined in the text as 75% limitation of ocular ductions.
PROPTOSIS WITH THIRD AND SIXTH NERVE PALSY

FIG. 1. Frequency distribution of the amount of relative proptosis measured in 40 control subjects. By convention, a positive value implies that the right eye was proptotic relative to the left eye.

DISCUSSION

The results of this study confirm that acute neurogenic ophthalmoplegia is not associated with a significant degree of axial orbital proptosis, as measured using the Hertel instrument. Proptosis greater than 1 mm is rare in that setting. The main conclusion of this study should be tempered by methodologic issues that may have introduced unintentional bias. For example, the measurements were made in an unblinded fashion. There was no practical way to employ a blinded examiner in this study for two reasons. First, the patient’s ophthalmoplegia would have been obvious to the examiner as he was performing exophthalmometry measurements. Second, the measurements obtained by a blinded examiner may have correlated poorly with those obtained by the author. Musch and colleagues (7) demonstrated that Hertel exophthalmometry is subject to large interobserver variability. In this study, interocular measurements in patients and controls were performed by one examiner using a standardized technique, features that likely minimized methodologic variability. In an office setting, each physician uses an exophthalmometry instrument the same way with all patients. Therefore, the conclusions reached in this study are applicable for anyone who uses the Hertel instrument in a consistent manner.

A control group was incorporated into this study mainly to ascertain the degree of interocular variability that would be measured using this technique in the author’s hands. Because the interocular difference of axial proptosis was the endpoint variable recorded in this study, there was no need to control age, gender, or other patient factors in the control population because these variables do not influence the interocular degree of axial proptosis (8).

The ocular deviation present in many of the patients, especially those with third nerve palsy, prevented them from fully shifting their gaze into the position requested. However, all patients were instructed to shift their gaze in the same manner so that this variable was minimized within each patient population. Although this inability to fully position some eyes into forward gaze might decrease the amount of protrusion measured in those patients, this should not detract from the conclusion of the study because, from a practical point of view, this is how proptosis is determined in clinical practice. The influence of this variable was likewise minimized in the current study by asking all patients and control subjects to fix upon a standard reference point.

In conclusion, the results of this study confirm what seasoned clinicians likely already know—identification of 2 mm or more axial proptosis in an ophthalmoplegic eye is more consistent with a restrictive, not neurogenic, etiology. Until now, however, this clinical dictum was based upon anecdotal experience only and had not been substantiated by a formal investigation.

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Epileptic Periodic Alternating Nystagmus

Mark L. Moster, M.D., and Eric Schnayder, M.D.

A patient developed periodic alternating nystagmus, periodic alternating gaze deviation, and periodic alternating head rotation as a manifestation of a seizure. This occurred as he awakened after hypoxic ischemic encephalopathy. Seizures should be added to the list of differential diagnoses of periodic alternating nystagmus.

Key Words: Periodic alternating nystagmus—Epilepsy—Encephalopathy—Epileptic nystagmus.

Periodic alternating nystagmus (PAN) is a horizontal jerk nystagmus that reverses direction in a cyclic manner, with intervening periods of ocular rest (1). It is most frequently caused by acquired lesions of the vestibular nuclei, the vestibulocerebellum, and the craniocervical junction. Periodic alternating gaze deviation has been seen in acquired brainstem disorders (2,3). Alternating head deviation may accompany either entity.

Nystagmus from focal epilepsy has been described (1,4) and usually consists of unilateral horizontal jerk nystagmus, most frequently beating contralateral to the lesion. We present a case of occipital lobe seizure that mimicked PAN.

CASE REPORT

A 68-year-old man was seen after coronary artery bypass graft and aortic valve replacement had been complicated by postoperative mediastinal hematoma, severe hypotension, and delayed awakening. Initial examination revealed him to be obtunded with intact brainstem reflexes. The following day he responded to painful stimuli and occasionally followed simple commands. He had normal lower extremity strength, but had severe upper extremity weakness and bilateral Babinski responses. Eye movements and pupils were normal. He was diagnosed with hypoxic ischemic encephalopathy and bilateral watershed infarcts between the anterior and middle cerebral artery circulations, accounting for bilateral arm weakness. Later that day, a generalized seizure was treated with intravenous phenytoin.

During the next day, he developed unusual eye movements. On examination, he was extubated, awake, followed simple commands and answered with appropriate simple sentences. Periodically he moved his eyes and head as follows: eyes deviated to the right with jerk nystagmus to the right for 1 minute. During this time, his head slowly moved to the right. Nystagmus then subsided, and his head returned to midline, followed by his eyes. After 10 seconds, he exhibited jerk nystagmus to the left, followed by slow deviation of his head 45° to the left. After 1 minute, gaze returned to midline with disappearance of nystagmus for 10 seconds.

The described phenomenon was observed for approximately 10 cycles. He remained awake and able to follow simple commands. He could not cooperate in visual field testing but appeared to respond to stimuli in all four visual field quadrants. Upper extremity strength had improved to normal.

Serum phenytoin level was therapeutic at 18.6 µg/ml. Baclofen was initiated, with no effect on eye movements. The following day, he underwent an EEG and was noted to have two spells of right-beating nystagmus during the procedure, corresponding to a left occipital seizure with gradual generalization over both hemispheres. The patient was described as alert but confused during the these episodes.

Oragapan was administered and periodic eye movements disappeared by the following day. Magnetic resonance imaging findings were normal and repeat EEG showed resolution of seizure activity. Mental status continued to improve, and he was discharged on the 12th hospital day. Neurologic examination 5 months later was unremarkable. Computed perimetry showed no hemianopia.

DISCUSSION

Epileptic nystagmus is a rare phenomenon, most often accompanied by horizontal jerk nystagmus with quick phases and gaze deviation away from the side of the seizure (1,4). Patients alert at the onset of nystagmus usually have a focal seizure emanating from the junctional region of the temporoparieto-occipital cortex.

In contrast to unilateral jerk nystagmus, our patient
had PAN, periodic alternating head rotation, and periodic alternating gaze deviation as manifestations of a focal onset seizure. Unfortunately, EEG recording was not obtained when the patient was seen clinically, and careful clinical examination was not performed during the EEG. Therefore, the exact mechanism of this epilepsy-induced phenomenon is unclear.

However, based on the clinical observations and course, we concluded that a focal seizure in the left occipital lobe accounted for head and eye rotation and right-beating nystagmus. When the seizures spread to the right occipital lobe, the nystagmus calmed and then reversed direction. When the seizure generalized, nystagmus stopped altogether.

Episodes of PAN occur in various clinical situations, including acquired lesions of the cranio-cervical junction, vestibulocerebellar pathways or brainstem, multiple sclerosis, cerebellar degeneration, Creutzfeldt-Jakob disease, infarction, trauma, encephalitis, neurosyphilis, visual loss, anticonvulsant toxicity and hepatic encephalopathy and as a variant of congenital nystagmus (1,5-9). We now add focal seizure to this list of causes of PAN. Therefore, in the appropriate clinical setting, patients with unusual patterns of nystagmus should have an EEG as a part of their evaluations.

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LETTERS TO THE EDITOR

To the Editor:

We are writing in response to the paper by Miki et al. regarding functional magnetic resonance imaging (fMRI) of the occipital cortex in the presence of postpapilloedematous optic atrophy (1). The visual field illustration using automated threshold perimetry demonstrates retention of central islands of vision, left greater than right, with sparing of at least 10° of the left visual field. However, on stimulation of each eye using a flashing checkerboard at 8 Hz, no activation was produced in the striate cortex but only in the extrastriate cortex. According to the revised representation of the visual field in the occipital cortex hypothesis (2,3), stimulation of the left visual field should have resulted in some activation of at least 50% of the right striate cortex posteriorly. During our own studies in 12 normal healthy volunteers using fMRI we have demonstrated activation both of the striate and extrastriate cortex on stimulation of the central 11° of the visual field using a similar checkerboard at 8 Hz (unpublished data). We therefore believe that the authors' claim that this patient's fMRI corresponded to the clinical features is not well founded.

Possibly their failure to activate the striate cortex in the presence of extrastriate activation is a reflection of the use of a slice thickness of only 6 mm, given the anatomical variations of the calcarine fissure, and the small number (only three) and duration (not quantified) of the stimulation periods. The latter is an important parameter during activation studies, as prolonged stimulation results in a habituation-like response in the visual cortex with a decrease in the activation signal (4). Furthermore, the activated image in their Fig. 3 includes the superior rim of the cerebellum, which in conjunction with the roundness of the image appears to indicate that the activated slice was obtained at a steeper angle than the one usually employed to include the calcarine fissure. Unfortunately, a reference sagittal scan is not available for comparison. Thus, it may be that the activated slice does not even include the posterior striate cortex.

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Authors' Reply

To the Editor:

We appreciate the comments of Drs. McFadzean and Condon. However, we have some disagreements with their interpretation of our results.

In our paper, we did not state the right striate cortex of the patient had not been activated at all. The activated areas by flash stimulus are thought to be 'primitive' visual areas. Therefore, we think these areas in the occipital pole and medial occipital lobe included the striate cortex although we are not certain if they also contained V2.

We selected the slice for the functional MRI after we identified the calcarine fissure in the midsagittal 'pilot' MR image. We believe our slice selection was adequate for the imaging of the calcarine cortex. In fact, we had performed functional MRI using the same slice thickness and orientation as this study in normal subjects and patients with visual deficits (1). In that study, we found good activation of striate cortex in normal volunteers. However, the calcarine fissure varies between individuals and sometimes winds considerably. In such cases, it may be difficult to examine the entire striate cortex by a single slice ('patchy appearance' (1)), and adjacent slices may also be necessary for the imaging of the striate cortex. Therefore, without a study which examines all of calcarine cortex, it is difficult to perform a 'precise' retinotopic correlation.

Additionally, a rest/stimulus cycle duration for this study is 83 seconds. This cycle duration seems to have been appropriate for the study (2).

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