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Bilateral Optic Neuropathies with Remission in Two HIV-Positive Men

Nancy J. Newman, M.D. and Simmons Lessell, M.D.

Two patients seropositive for the human immunodeficiency virus (HIV) developed bilateral optic neuropathies. Evaluations failed to identify an infectious or neoplastic etiology. Both patients improved, one in temporal relation to treatment with azidothymidine (AZT), the other during oral steroid therapy. Optic neuropathy in HIV-positive patients does not necessarily carry a poor prognosis even when a treatable cause is not found. A role for primary HIV infection in the pathogenesis remains speculative.

Key Words: AIDS—HIV—Optic neuropathy.

CASE STUDIES

Case 1

A 39-year-old homosexual man was referred because of bilateral visual loss. His medical history was notable for a psychiatric disorder characterized by auditory hallucinations for which he received thiothixene hydrochloride and nortriptyline hydrochloride. Eighteen months before presentation he was discovered to be HIV-positive. He smoked one pack of cigarettes per day. There was no personal or family history of ophthalmic or neurologic disease.

Ten days before referral, he awoke with bilaterally blurred vision and slight retrobulbar pain aggravated by eye movement. His vision gradually failed, and he was evaluated at a local hospital. Acuity was then best correctible to 20/30 bilaterally, and ophthalmoscopic examination was normal. General physical examination, complete blood count, urinalysis, serological test for syphilis, and head computerized tomographic (CT) scan were normal. Cerebrospinal fluid (CSF) analysis revealed 17 white blood cells/mm³ and 120 mg of protein/100 cc. Within 1 week, vision deteriorated to 20/400 OD and finger counting OS.

Optic nerve disease in patients infected with the human immunodeficiency virus (HIV) may occur secondary to opportunistic infections or neoplasms (1-15). We report on two HIV-positive men with bilateral retrobulbar optic neuropathies that subsequently improved and in whom no specific infectious or neoplastic etiology other than the HIV virus was implicated.
fixation OD. A left relative afferent pupil defect was evident. The rest of his eye, general physical, and neurological examinations revealed no abnormalities.

His hematocrit was 34.5, and the total WBC was 4,900 with a normal differential. Cerebrospinal fluid contained 24 white blood cells and six red blood cells/mm$^3$. The white cells were plasmacytoid with surface markers characteristic of a reactive pleocytosis. The protein content was 115 mg%. Cryptococcal antigen was negative, and cultures for bacteria, mycobacteria, and fungi grew no organisms. Blood and CSF VDRL and FTA-Abs tests were negative. Serum vitamin B12 level was normal. No abnormalities were seen on a magnetic resonance image (MRI) scan of the head with gadolinium injection, but both optic nerves appeared thickened on a CT scan. Mitochondrial analysis of his blood failed to reveal the 11,778 point mutation associated with Leber's hereditary optic neuropathy.

He received oral prednisone 60 mg/day for 1 week followed by rapid tapering without noticeable benefit. Similarly, 2 weeks of intravenous penicillin did not appear to help. Azidothymidine (AZT) was begun 4 weeks after the onset of symptoms at a dose of 100 mg $\times$ 5/day. Within 10 days, he noticed some improvement in his vision, and acuity was measured as 3/200 OD and 2/100 OS. Slight optic disc pallor was apparent for the first time. Eight weeks after the onset of symptoms, visual acuity was 5/70 OD and 5/40 OS. Four months after the onset of symptoms, his vision had improved to 13/200 OD and 20/70 OS. Visual fields showed bilateral relative central scotomas, and ophthalmoscopic examination revealed pronounced optic atrophy. Eight months after onset, visual acuity stabilized at 20/70 OD and 20/40 OS.

Case 2

A 27-year-old homosexual man was referred because of bilateral visual loss. Five months earlier, he complained of generalized fatigue followed by left leg weakness and numbness. He was discovered to be HIV-positive, and an HIV-associated myelopathy was diagnosed. An MRI of the cervical spinal cord was normal. CSF analysis revealed a protein of 68 mg%, glucose of 48 mg%, and 29–50 white cells (97–99% lymphocytes). Cryptococcal antigen and cultures for bacterial, mycobacterial, and fungal organisms were negative. CSF and serum VDRL and FTA-Abs were nonreactive, but CSF and serum antibodies to HIV and cytomegalovirus (CMV) were present. He was begun on AZT. The patient did not use cigarettes, alcohol, or recreational drugs. There was no personal or family history of ophthalmologic or neurologic disease.

Four months before referral, the patient’s vision OD suddenly decreased, and there was eye pain aggravated by eye movement. No funduscopic abnormalities were noted; acute retrobulbar optic neuritis was diagnosed. The vision remained poor, but stable, in the right eye. An MRI of the brain was normal except for one small bright lesion without mass effect adjacent to one of the lateral ventricles. Approximately 3 months later, the patient noted blurring of vision OS, also with accompanying mild discomfort on eye movement. Repeat CSF analysis revealed a protein of 81 mg%, glucose of 47 mg%, and 15 white cells. IgG was elevated, and the VDRL, cryptococcal antigen, and cultures were negative. The patient’s vision progressively deteriorated over the next month, and intravenous gancyclovir was begun as empirical therapy for CMV.

The patient was referred for neuroophthalmologic examination 4 months after the onset of visual loss OD, 1 month after onset of symptoms OS. Visual acuity was hand motions perception superonasally OD and 20/200 OS. Colors were grossly identified OS. Goldmann visual fields demonstrated a temporal island of vision to the V4e stimulus OD and an inferior defect with central involvement OS. There was a right relative afferent pupil defect. Slit lamp biomicroscopy was normal. Ophthalmoscopic examination revealed temporal pallor of the right disc and possibly early pallor of the left disc.

The patient was continued on AZT and intravenous gancyclovir and also received a 2-week course of intravenous penicillin. Vision continued to slowly deteriorate OS. One month after referral, 60 mg oral prednisone was started. Although the patient had noted some improvement in the vision OD before the initiation of steroids, he reported definite improvement in vision OD 3 days after the prednisone was begun. This improvement continued, plateaued with an attempt to taper the steroids, and resumed when the prednisone dose was increased. An examination 3 weeks after the prednisone was begun showed acuities of 10/200 OD and 4/200 OS. Goldmann visual fields demonstrated a relative central scotoma OD and a dense central scotoma to the V4e stimulus OS. There was now a left relative afferent pupil defect, and both optic discs were pale. Over the next month, vision gradually improved to 20/30 OD and 20/40 OS. Steroids and gancyclovir were discontinued, and AZT was maintained. There was no change in his vision over the next 4 months.
DISCUSSION

HIV-associated optic nerve disease may occur secondary to compressive, infiltrative, infectious, inflammatory, or vascular etiologies (1-16). Although neoplasms occur with great frequency in HIV-positive patients, compressive and infiltrative lesions of the optic nerve are relatively rare (17-22). Lymphoma is found infrequently in the orbit; but intracranial lymphoma, toxoplasmosis, or eosinophilic granuloma can cause anterior visual pathway dysfunction (19-21,23). Opportunistic infections underlie the majority of optic neuropathies associated with HIV. Syphilitic infection can result in unilateral or bilateral retrobulbar optic neuropathies, papillitis, or optic perineuritis (1,2,4-6). Standard clinical or laboratory evidence of treponemal infection may be absent or altered by concurrent HIV infection (24-26). This phenomenon has prompted many authorities to recommend, on an empirical basis, penicillin trials at neurosyphilis doses in patients with optic neuropathies of unclear origin (1,24,27). Similarly, the natural history and response to treatment of syphilitic optic neuropathy may be altered by HIV infection (1,24,26). Cryptococcal meningitis can result in optic neuropathies, presumably on the basis of perineuritic adhesive arachnoiditis (7). Although the cytomegalovirus has been isolated in optic nerve tissue (9) and implicated in profound visual loss most consistent with optic neuropathy (8), concurrent CMV retinitis or papillitis is the rule (8,9). Toxoplasma gondii, although a common cause of intracranial infiltrative disease in patients with AIDS, rarely involves ocular structures (10,20). As is the case with CMV, when toxoplasma optic nerve infiltration occurs, simultaneous retinochoroiditis is prominent. Herpes zoster has been implicated in at least three cases of optic neuropathy with papillitis, only one responsive to acyclovir (1,11,12). Hepatitis B may similarly result in papillitis (13). Although progressive multifocal leukoencephalopathy (PML) is a common cause of cerebral white matter lesions in AIDS patients, involvement of the prechiasmal visual pathways by the JC papova virus has yet to be described. Primary HIV infection has been postulated as the underlying mechanism in one case of presumed anterior ischemic optic neuropathy (16) and in a case of optic neuritis that did improve (14), but it is likely that the latter case represented reactivation of neurosyphilis with papillitis.

In our patients, neuro-imaging excluded compressive etiologies. The absence of disc edema and associated retinochoroiditis made infectious causes such as CMV and toxoplasma unlikely. The isolated involvement of the optic nerves and the eventual recovery of vision argued against PML, although there is at least one report of spontaneous improvement in AIDS patients with biopsy-proven PML (28). Cryptococcal meningitis may rarely be antigen negative (29). However, the lack of other systemic and neurologic symptoms and signs, and the recovery of vision without specific antifungal treatment in our patients made this an unlikely diagnosis. Syphilis must be considered in any retrobulbar optic neuropathy, especially in patients infected with the AIDS virus. Our patients had both cerebrospinal fluid pleocytosis and elevated protein, nonspecific findings that are not inconsistent with neurosyphilis. There were no other neurologic or systemic findings suggestive of treponemal infection, and repeated serum and CSF analysis failed to provide laboratory confirmation of this diagnosis. It must be emphasized that HIV-positive patients may have nonreactive serum and CSF VDRLs (24-26). Both of our patients received treatment for neuro-syphilis with intravenous penicillin (an empirically based decision). Neither patient was recovery coincident with antibiotic treatment.

HIV has been directly implicated in the pathogenesis of neurologic and ophthalmologic disease (30-36). This neurotropic virus is capable of establishing latency in the nervous system early in its course (30,33,36,37). HIV has been isolated, and immunocytochemical and in situ hybridization studies have demonstrated the presence of viral antigens and nucleic acids in neural and ocular tissues from patients with AIDS (33,35,36,38-40). Cerebral lesions are found predominantly in the subcortical white matter (31).

Proposed mechanisms of HIV-mediated disease include direct viral infection, HIV-mediated vasculitis, postviral-mediated immune attack on neural components, or autoimmune destruction of neural or vascular structures secondary to abnormal immunoregulation caused by the primary HIV infection (41). Primary HIV infection has been implicated in the pathogenesis of the AIDS dementia complex, vacular myelopathy, peripheral neuropathies, and cranial neuropathies (30,31,41-43). These manifestations may coincide with HIV seroconversion, may be the only clinical indication of chronic HIV infection, or may be part of the full clinical picture of AIDS (30,41). Isolated facial paralysis, for example, is frequently associated with HIV seroconversion and usually improves spontaneously (42,43). An acute demyelinating polyradiculopathy similar to Guillain-Barre and a more
chronic demyelinating polyneuropathy have been linked to primary HIV infection (41,42). They may be responsive to steroids, plasmaphoresis, or AZT (41,42,44).

Of course, it is possible that our patients' bilateral optic neuropathies were entirely unrelated to HIV infection. Patients in this age group may suffer idiopathic acute or subacute optic neuropathies, occasionally bilateral. The typical course is that of progressive loss of central vision over days with eye pain, and spontaneous improvement after weeks or a few months, not the prolonged progression and recovery demonstrated by our patients. However, series of patients with idiopathic bilateral optic neuropathies and prolonged progressive deterioration, some of whom also eventually recovered their vision, have been described (45,46).

Multiple sclerosis-like illnesses have been reported in HIV-positive patients, and in several cases, an etiologic association was postulated (47,48). Three of the patients described by Berger et al. (47) had HIV seropositivity demonstrated within 3 months of the onset of their neurologic disease, and all three had optic neuritis as part of their clinical picture. Improvement in vision was the rule in all cases, in two without medical treatment, in one after steroid therapy.

Our second patient had a myelopathy followed by sequential bilateral optic neuropathies and a single small white matter lesion on MRI. His optic neuropathies were atypical for optic neuritis, but clinically, his findings are not inconsistent with the diagnosis of multiple sclerosis. Although the patient was on several medications, his symptomatic recovery was most closely related temporally to steroid therapy. In contrast, our first patient had no other neurologic symptoms or signs, a normal MRI, and no improvement in vision related to a prednisone trial. His visual recovery was most temporally related to treatment with AZT. In both cases, the possibility of spontaneous recovery cannot be dismissed.

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Rapid Response of Syphilitic Optic Neuritis to Posterior Sub-Tenon's Steroid Injection

Robert L. Tomsak, M.D., Lisa D. Lystad, M.D., M. Bashar Katirji, M.D., and Thomas C. Brassel, M.D.

An HIV-positive man with subacute syphilitic meningitis developed severe bilateral visual loss from optic neuritis. His visual acuity improved remarkably within 24 hours after single posterior sub-Tenon's injections of triamcinolone (Kenalog) were given. Periocular steroid injections should be considered as an adjunctive treatment of syphilitic optic neuritis.

Key Words: Neurosyphilis—Human immunodeficiency virus—Optic neuritis—Periocular steroids.

Zambrano et al. (1) described an AIDS patient with bilateral blindness from retrobulbar syphilitic optic neuritis whose vision slowly improved in one eye over 2.5 months during and after intravenous (i.v.) penicillin therapy. Herein we describe a similar patient in whom remarkable visual improvement occurred within 24 hours after single posterior sub-Tenon's steroid injections.

CASE REPORT

A 56-year-old black man was admitted to the University Hospitals of Cleveland for intravenous treatment of subacute syphilitic meningitis. Two months before admission he developed slowly progressive visual loss in both eyes, greater in the right than in the left, and began to have difficulty walking. One month before admission, he was diagnosed with bilateral uveitis and was treated with topical ophthalmic steroid and cycloplegic eye drops. He had a reactive serum VDRL with a titer of 1:64 and tested positively for HIV-1 at that time.

Physical exam was remarkable for a hyperpigmented rash with desquamation on both palms and soles. Neurologic exam showed mild truncal ataxia, a partial right peripheral facial palsy, and mild hearing loss bilaterally. Serum FTA-ABS was reactive on admission, and spinal fluid examination showed 69 white cells, predominantly lymphocytes, a protein of 126 mg/dl, a glucose of 41 mg/dl (serum glucose 120 mg/dl), and a reactive VDRL (titer not done). Neuro-ophthalmologic examination on August 7, 1991, after 40 million units of IV penicillin (4 million U i.v. every 4 hours) disclosed visual acuities of no light perception (NLP) OD and hand movements (HM) at 3 feet OS. A partial right peripheral seventh nerve palsy was present. Both pupils were pharmacologically...
dilated. Slit lamp exam showed moderate cells and flare OD and mild flare OS. The right vitreous was hazy because of a moderately severe cellular infiltrate, and 1+ cells were also present in the left vitreous. Both optic discs were slightly swollen. The retinal details on the right were obscured by the vitreous haze, but there were no signs of cytomegalovirus retinitis or other obvious abnormalities. Aside from the optic disc, the left fundus appeared normal. The visual dysfunction was too severe to be explained by the media haze, and syphilitic optic neuritis and uveitis were diagnosed.

The patient was given bilateral posterior sub-Tenon's injections of triamcinolone acetonide (Kenalog) (E. R. Squibb & Sons Inc., Princeton NJ) 40 mg by the method of Smith and Nozik (2). The following day, vision had improved to light perception with projection OD and 20/50 OS (Table 1). By August 23, 1991, visual function was 20/40 minus OD and 20/25 – 2 OS. Visual fields by Goldmann technique showed a peripheral inferior altitudinal defect OD and bilateral blind spot enlargement greater in the right than in the left.

During hospitalization, the patient received a total i.v. dose of 432 million U penicillin. Serologic followup on August 29, 1991, showed an unchanged serum VDRL titer of 1:64. Spinal fluid VDRL was nonreactive on September 19, 1991.

**DISCUSSION**

There is some evidence that periocular triamcinolone injections hasten visual improvement, but not ultimate visual acuities, in idiopathic optic neuritis, especially during the first week after injection (3). Improvement of vision within days of administering methylprednisolone i.v. to optic neuritis patients has also been reported (4). However, the rapid visual improvement demonstrated by our patient following posterior sub-Tenon's triamcinolone injections was unusually dramatic.

The pathogenesis of syphilitic optic neuritis includes inflammatory and demyelinating events, sometimes leading to optic atrophy (1). Our patient's rapid visual response suggests that some of these processes are steroid sensitive. Posterior sub-Tenon's steroid injections should be considered as an adjunctive treatment of syphilitic optic neuritis.

**Note:** The patient was last seen 12/18/91 with visual acuities of 20/40 OD and 20/25 OS. The uveitis had cleared completely.

**REFERENCES**

Rapid Response of Syphilitic Optic Neuritis to Posterior Sub-Tenon's Steroid Injection and Bilateral Optic Neuropathies with Remission in Two HIV-Positive Men

The two papers in this issue, the first by Newman and Lessell and the second by Tomsak, Lystad, Katirji, and Brassel, impress us with the fact that neuro-ocular syphilis is a disease that not only won't go away but continues to present ever increasing challenges—both diagnostic and therapeutic—to the clinician.

Pertinent to the paper “Bilateral optic neuropathies with remission in two HIV-positive men” is an extremely important report by Haas et al. (1) from the Department of Medicine, University of California, the San Francisco Department of Public Health, and from the Centers for Disease Control in Atlanta. The term “serological test for syphilis” is really inadequate because there are many different blood tests used in the serodiagnosis of this disease. However, the tests fall into two basic groups. In the first are the reagin, or nonspecific, tests, the RPR (rapid plasma reagin) or VDRL being the two most commonly used at this time. In the second group are the treponemal, or specific, tests, with the FTA-ABS (fluorescent treponemal antibody absorption) and the MHA-TP (microhemagglutination assay for antibodies to Treponema pallidum) being the two most frequently used in this country. Another specific test, the TPI (Treponema pallidum immobilization), is difficult to obtain in the United States at this time. It is known that over 90% of persons infected with syphilis will continue to have reactive test results with the treponemal tests even after adequate therapy. Many clinicians consider that a nonreactive treponemal test (i.e., FTA-ABS or MHA-TP) shows that there was no prior syphilis infection; this is a good general rule, although there have been rare exceptions reported.

However, Haas et al. (1) performed an extremely valuable study that should be carefully scrutinized by an physician encountering neuro-ophthalmological patients. They studied two groups of homosexual men who had serum samples stored in the University of California AIDS serum bank. One group had symptomatic HIV infection and had been followed between 1982 and 1985. The other group were either HIV seronegative or seropositive but were asymptomatic in 1983–1984. The records of all patients with a self-reported history of syphilis were reviewed retrospectively. Patients were included in this study if their history of syphilis could be documented by records maintained in the San Francisco Department of Public Health. Patients were excluded if their history of syphilis was not so documented, if there were no records of a previously reactive treponemal test, or if a treponemal test had not been done on entry into the serum bank. The Department of Public Health maintains records of all syphilis cases reported in San Francisco County since 1975.

Of 324 persons in the two longitudinal studies, 191 gave a self-reported history of syphilis. Seventy-eight individuals were excluded because a prior episode of syphilis was not documented by the Department of Public Health. The syphilis serology of 109 homosexual men with a documented history of treated syphilis was compared with records of prior results and confirmed on stored
EDITORIAL COMMENT

Ocular penetration of erythromycin after injection in subtenon’s space

J. L. Smith, M.D.
Editor
Miami, Florida

<table>
<thead>
<tr>
<th>Sample</th>
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<tr>
<td>Serum</td>
<td>0.23 µg/ml</td>
</tr>
<tr>
<td>Vitreous humor</td>
<td>0.93 µg/ml</td>
</tr>
<tr>
<td>Vitreous humor</td>
<td>1.20 µg/ml</td>
</tr>
<tr>
<td>Optic nerve</td>
<td>35.0 µg/g</td>
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Although a different pharmacologic agent was used for this bioassay (i.e. an antibiotic rather than a steroid drug), the detection of a tissue level more than 30 times as high in the optic nerve itself as compared to the intraocular fluids 75 minutes after a subtenons injection, certainly establishes the fact that this route of administration can effectively give high tissue levels of a pharmacologic agent in the optic nerve itself.

The “take home” lesson from the Haas and Tomsak studies is simply this—don’t be satisfied with a serum VORL and a serum FTA-ABS test on your patient. Take a meticulous history asking specifically for prior venereal infections with emphasis on syphilis.

If the latter history is positive, you should strongly consider treating the patient for syphilis, particularly if the amount of therapy is in doubt and particularly if the patient is HIV-positive. In the patient on intravenous penicillin therapy for syphilis, concomitant administration of 1 cc of aqueous triamcinolone (Kenalog) by the subtenon’s route, using a #25 needle, 5/8” long, may be an important adjunct in the total treatment regimen.

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REFERENCES

Visual Recovery in Patients with Leber’s Hereditary Optic Neuropathy and the 11778 Mutation

Edwin M. Stone, M.D., Ph.D., Nancy J. Newman, M.D., Neil R. Miller, M.D., Donald R. Johns, M.D., Marie T. Lott, M.A., and Douglas C. Wallace, Ph.D.

Five patients with Leber’s hereditary optic neuropathy (LHON) and the 11778 mitochondrial mutation spontaneously recovered 20/40 or better visual acuity in at least one eye after months to years of legal blindness. The patients ranged in age from 9 to 45 years, and the duration of visual loss before recovery ranged from several months to 5.9 years. These patients constitute only about 4% of the 136 affected LHON patients we have studied who also had the 11778 mutation in their mitochondrial DNA. Thus, even though the visual prognosis for most patients with LHON and the 11778 mutation is poor, a few individuals do recover near-normal vision in at least one eye even years after the initial visual loss.

Key Words: Leber’s hereditary optic neuropathy—11778 Mitochondrial mutation.
TABLE 1. Summary of visual acuity

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>O.D.</th>
<th>O.S.</th>
<th>O.D.</th>
<th>O.S.</th>
<th>Duration of binocular loss</th>
</tr>
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<tr>
<td>1</td>
<td>45</td>
<td>20/400</td>
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<tr>
<td>5</td>
<td>15</td>
<td>20/400</td>
<td>20/400</td>
<td>20/30</td>
<td>CF 4</td>
<td>1 year</td>
</tr>
</tbody>
</table>

CF, count fingers.

* Surgical injury of left optic nerve during craniotomy.

§ Persistent hyperplastic primary vitreous and cataract present at birth.

The patient was referred to another ophthalmologist who noted count fingers vision at 6 feet O.D. He was admitted to the hospital for evaluation, but the only abnormality that was found was 80 mg% protein in the cerebrospinal fluid (CSF) (normal 40-45 mg%). In October 1970, 10 months after his initial visual loss, the visual acuity in the left eye began to change and dropped steadily to 20/70 over the next eight months. Central scotomas were present in both eyes. Retrobulbar neuritis was diagnosed and steroid treatment was begun. There was no improvement after 4 months of treatment.

The patient was examined at regular intervals over the next 3 years, during which time his vision initially worsened and then stabilized. In August 1989, the visual acuity was still 6/200 O.U., color vision was markedly diminished in each eye, and there were large central scotomas. Both optic discs were diffusely pale. The patient's blood was found to be homoplasmic for the 11778 mutation. During the summer of 1990, the patient began to experience improvement in visual func-
tion in both eyes. He was seen in October 1990, 4.5 years after the initial onset of visual symptoms, at which time his visual acuity had improved to 20/30 O.D., and 20/400 O.S. The central scotomas had decreased markedly in size. Both optic discs remained pale.

Case 3

A 12-year-old boy born with persistent hyperplastic primary vitreous (PHPV) and cataract O.D. experienced blurred vision O.S. This progressively worsened over the next 3 months to an acuity of 5/200. Absent color vision, a large central scotoma (Fig. 1, panel A) and optic atrophy were documented. The results of an extensive evaluation including a brain CT scan with and without cisternography, brain MRI, (ERG) and electrocardiogram (EKG) were normal. Visually evoked responses were absent. The patient's medical history was also notable for mild growth retardation and sexual immaturity. Family history was negative for visual loss. Thirty months later, the patient had the sudden onset of a “flash” in his left eye, followed 1 hour later by the ability to see well with his left eye. An examination revealed visual acuity of 20/25 O.S. and normal color vision. The Goldmann visual field O.S. continued to show a large dense central scotoma, but within the center was an approximately 2-degree area of intact visual field and acuity (Fig. 1, panel B). The optic disc was profoundly atrophic. The blood of the patient and several maternally related family members was found to be homoplasmic for the 11778 mitochondrial DNA mutation.

Case 4

A 9-year-old girl presented with bilateral visual loss that progressively deteriorated over 1 month to 20/200 O.U. Errors in color vision and central visual field defects were noted. Ophthalmoscopic examination was remarkable for optic disc pallor. An evaluation included a normal brain MRI and CSF analysis, and an “inconclusive” muscle biopsy. She was found to have previously unrecognized insulin-dependent diabetes mellitus and was treated accordingly. Family history was notable for several maternal relatives with permanent bilateral visual loss that occurred in their 30s secondary to LHON. Blood samples from the patient and maternally related family members were homoplasmic for the 11778 mutation. Several months later, the patient noted gradual improvement in visual acuity in first the left, then the right, eye. At the most recent examination, she was 20/40 O.U. Her optic discs remain profoundly atrophic.

Case 5

A 15-year-old boy experienced decreased vision in his left eye, which progressively deteriorated over months. An ophthalmologic examination was normal, and the patient was diagnosed as having
factitious visual loss. After 8 months of psychotherapy, the vision in the right eye began to fail. Six months later, his visual acuity was 20/400 O.U., and optic atrophy was noted. Visual evoked responses revealed increased latency. A brain MRI and brainstem-evoked potentials were normal. The patient's medical history was negative, and his family history was unremarkable for visual loss except for his maternal grandmother, who had cataracts and glaucoma. An examination of the patient's blood revealed it to be homoplasmic for the 11778 mutation. Approximately 1 year after the onset of visual loss in the right eye, the patient noticed gradual improvement in the central acuity of the right eye over several weeks. An examination revealed visual acuities of 20/30 O.D. and count fingers at 4 feet O.S. There was no relative afferent pupillary defect. Goldmann visual fields showed bilateral central scotomas to approximately 20 degrees O.U., but within the scotoma O.D., there was central sparing of vision of about 5 degrees. His optic discs showed optic atrophy temporally, and there was loss of nerve fiber layer in the papillomacular bundles of both eyes.

**DISCUSSION**

It has long been recognized that a small subset of patients with LHON eventually recover a substantial amount of central visual acuity (6-9). However, before the identification of a specific, assayable causative mutation, the diagnosis of LHON was rarely certain, and visual recovery in patients initially thought to have LHON raised the possibility of an incorrect diagnosis. With the identification of the 11778 mutation came the ability to make a firm diagnosis of LHON. The great majority of patients who lose their central vision as the result of the 11778 mutation do not recover it. In fact, the five cases described in this report represent only about 4% of the 136 11778 LHON patients who have been studied in our three institutions. Holt et al. (10) suggested that the 11778 mutation is incompatible with visual recovery. Our five cases demonstrate conclusively that patients with the 11778 mutation can recover vision.

The documentation of spontaneous visual recovery in patients with the 11778 mutation is important for several reasons. First, it allows us to discuss the small, but real, possibility of visual recovery with our patients in whom we identify the 11778 mutation. Second, it allows us to be certain that this very unusual pattern of visual recovery is in fact occurring in patients with bona fide LHON and not some other disease such as nutritional amблиопия that one would more readily expect to be associated with visual recovery. The percentage of our 11778 LHON patients who recovered vision is substantially lower than the 12-25% reported by other investigators (5,8,11) for groups of patients with the clinical diagnosis of LHON. This difference could be caused by a higher rate of recovery in patients with other mitochondrial mutations (3), but at least some of the discrepancy is probably caused by the accidental inclusion of non-Leber's cases in series that were gathered according to clinical criteria alone.

There are several additional noteworthy features of our five patients. In our experience, the most common incorrect diagnosis made in cases of LHON, especially during the period when only one eye is affected, is optic neuritis. Patients so diagnosed frequently receive steroids, often in large doses, without effect. The fact that large doses of steroids were given to our first patient without benefit, only to have his vision return spontaneously nearly 6 years later, strengthens our anecdotal clinical impression that steroids are of no benefit in this disease.

Two of our patients recovered vision by developing small islands of normal vision within their central scotomas as depicted in Fig. 1. This phenomenon was first noted by Hancock in 1908 (12). In 1970, Brunette and Bernier (11) published tangent fields with this finding from one of their Leber's patients who had recovered vision. In our experience, such fenestrated scotomas are characteristic of recovered LHON, and this diagnosis should be entertained whenever this visual field finding is present. The visual recovery in some of our patients was rather rapid and was signaled by flashing lights within the scotoma.

The mechanism of the visual recovery in these patients is, at present, wholly unknown. However, it is exciting to think that some of our patients with LHON might recover even 6 years after their visual loss. We are hopeful that further study of such patients will uncover some portion of the visual recovery mechanism that is amenable to medical intervention so that patients who have lost vision from LHON might be successfully treated.

**Acknowledgments:** The authors wish to thank Dr. Francis C. Dunn, Jr., for providing the clinical information and blood sample from Case 1. We thank Drs. Myles Behrens, Norman J. Schatz, and Steven E. Feldon for permission to use Cases 2, 3, and 4, respectively. Cases 3, 4, and 5 are designated Cases 60.01, 44.01, and 78.01, respectively, in Newman NJ, Lott MT, Wallace DC. The clinical characteristics of pedigrees of Leber's Hereditary Optic Neuropathy with the 11778 mutation. **Am J Ophthalmol 1991;111:750-762.**
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Evidence for a Metabolic Trigger for Leber’s Hereditary Optic Neuropathy

A Case Report

L. G. DuBois, m.ed., co, comt and S. E. Feldon, m.d.

A 9-year-old girl with recently diagnosed juvenile onset diabetes mellitus presented with signs and symptoms of bilateral optic neuropathy. Leber’s hereditary optic neuropathy was suspected on the basis of a strong family history. Subsequent mitochondrial DNA testing was positive. Visual recovery occurred once the diabetes was well controlled. This case suggests that such metabolic compromise that occurs in diabetes may precipitate the clinical expression of Leber’s optic neuropathy.

Key Words: Leber’s Disease—Mitochondria—Metabolism in Leber’s.
the time of presentation, the best corrected visual acuity was 20/200 OD and 20/200 OS; color vision was markedly reduced so that only 1 of 15 AO pseudoisochromatic plates were correctly identified for each eye. There was an enlarged physiologic blind spot in the visual field of the left eye, and there were central scotomata bilaterally. Temporal disc pallor was present on the right, and diffuse disc pallor was present on the left; if there had been early telangiectasis, it was no longer apparent. There was nerve fiber layer loss in both eyes. Electretinography, magnetic resonance imaging, and computed tomography were normal, but the visual evoked potential was abnormal. In addition to ophthalmologic symptoms, the patient had mild diffuse muscular weakness and was recently diagnosed as having juvenile onset diabetes mellitus; there was no indication of mitochondrial myopathy found on muscle biopsy, and a genetic probe was not performed.

The maternal family history was positive for clinically diagnosed Leber's in an aunt, a sister, and a male cousin. The patient's brother suffered from a muscular dystrophy of unknown etiology. The proband's blood and hair analyses were positive for the mDNA marker. Subsequent clinical and genetic evaluation of the three relatives, the proband's mother, and her brother supported a diagnosis of Leber's in all five, although not all had visual symptoms. Once hyperglycemia was stabilized with subcutaneous insulin administration, the patient recovered visual function within 9 months. Visual acuity improved to 20/25 OD and 20/60 OS; color discrimination improved to 7/15 AO pseudoisochromatic plates on the right and 4/15 plates on the left. The optic discs remained pale.

**DISCUSSION**

Based on the non-Mendelian inheritance pattern for mDNA, it may be postulated that variations in the number of mutant mitochondria or perhaps the proportion of mutations within a mitochondrion explains the variable expression of Leber's within a given family. It is presumed that the onset of the disorder signals the end of the mitochondria's ability to generate sufficient energy for enough cells to maintain "normal" visual function. During the period preceding the rapid decline in vision of a patient with Leber's, or during the lifetime of an asymptomatic "carrier" of the mutation, the deficiency in energy production by the mutant mitochondria might be partially compensated by the increase in nutrients delivered by telangiectatic vessels. Indeed, the telangiectasis of normally small vessels in the retina might be a response to the early degeneration of cells due to unmet energy requirements. If, in addition to a genetically fragile intracellular environment, the added insult of an external "hit" exists, then the cell may not be able to maintain its borderline viability. This, we believe, is the mechanism for the visual loss and subsequent recovery in the very young female Leber's patient in our case report.

The combination of genetic and metabolic alteration of mitochondrial respiration at the onset of diabetes in our patient may have initiated the onset of her neuropathy. Reestablishing the normal metabolic milieu with exogenous insulin probably restored the function of enough viable neurons to restore visual function. Although genetically normal cerebral tissue mitochondria are not metabolically affected by a chronic hyperglycemic, insulin-deficient condition, a change in mitochondrial anion transporter function is known to occur in diabetes and may affect the deregulation of transport proteins in coordination with metabolic enzymes (5, 6). In addition, substantial decreases (20-35%) in calcium ion uptake by mitochondria in diabetic rats have been reported (7), suggesting a loss in aerobic glucose oxidation.

The eventual mild improvement of visual function in patients with Leber's is well documented. The reversal of severe visual loss in our patient when her metabolic "trigger" for Leber's was discovered and treated suggests the existence of a precipitating, but treatable, environmental event. It therefore becomes important, with the early diagnosis of Leber's, to fully evaluate the patient in order to discover any treatable secondary condition such as anemia, toxicity, inflammation, and nutritional deficiencies. If an optimum cellular environment can be established, perhaps the visual consequences of Leber's will remain minimal or even improve to subclinical status.

**REFERENCES**

Acute VI\textsuperscript{th} Cranial Nerve Dysfunction In Multiple Sclerosis
Evaluation by Magnetic Resonance Imaging

John W. Rose, M.D., Kathleen B. Digre, M.D.,
Sharon G. Lynch, M.D., and Ric H. Harnsberger, M.D.

VI\textsuperscript{th} nerve palsy is not frequently considered a presenting sign of multiple sclerosis (MS); however, MS has been documented as a fairly common cause of VI\textsuperscript{th} nerve dysfunction. In the present study we have evaluated the clinical features and magnetic resonance imaging (MRI) findings in four MS patients with acute VI\textsuperscript{th} nerve palsy. Diplopia as a result of acute VI\textsuperscript{th} nerve palsy was the prominent symptom leading to the diagnosis of MS in all of the individuals. Other signs specifically localizing to the ipsilateral brainstem were absent in these patients. Cranial MRI revealed multiple white matter lesions with a periventricular predominance in all four patients and pontine white matter lesions in three of the patients. These lesions were either adjacent to the VI\textsuperscript{th} nerve nucleus or involved the fasciculus of the VI\textsuperscript{th} nerve or both.

Key Words: Magnetic resonance imaging—Multiple sclerosis—VI\textsuperscript{th} nerve palsy.

Disorders of extraocular motility, especially internuclear ophthalmoplegia and nystagmus, occur frequently in patients with multiple sclerosis (MS). Dysfunction of the VI\textsuperscript{th} cranial nerve is much less common. In fact, the appearance of an apparently isolated cranial nerve palsy is considered an unlikely presenting symptom in MS. Similarly, the new onset of such a deficit in a patient with established MS often raises questions about the original diagnosis. It is notable, however, that retrospective studies of patients presenting to the ophthalmologist with the new onset of VI\textsuperscript{th} nerve palsy demonstrate that up to 12% are diagnosed as having MS (1-4).

We describe the clinical features of four MS patients with acute dysfunction of cranial nerve VI. Magnetic resonance imaging (MRI) was able to demonstrate the responsible lesion in three of the four patients.

METHODS

All images were obtained on a 1.5 Tesla Signa MR scanner (General Electric, Milwaukee, Wisconsin, U.S.A.). TI weighted sagittal and axial series were done with a TR of 750 msec and a TE of 20 msec. Axial T2 weighted images were obtained with a TR of 2,800 msec and a TE of 70 msec in patients 1, 2, and 4. Axial images were obtained with a TR of 2,333 msec and a TE of 30 msec in patient 3. All axial images were performed with a 5 mm slice thickness and an interslice gap of 3.5 mm.

CLINICAL SUMMARIES

Case 1

A 24-year-old white woman developed tinnitus, associated with decreased hearing on the right, but
she did not seek medical attention until 3 weeks later when she had the onset of diplopia. The patient subsequently developed numbness and paraesthesias of the right upper extremity. Neurologic examination revealed a complete left cranial nerve VI palsy, sensorineural hearing deficit on the right, hyperreflexia in the left upper and both lower extremities, and bilateral extensor toe signs. Cerebrospinal fluid (CSF) protein was 64, and oligoclonal bands were present. The WBC in the CSF was 13/mm$^3$ with a differential of 97% lymphocytes and 3% mononuclear cells. An MRI demonstrated multiple white matter abnormalities in the cerebral hemispheres and a focal area of increased signal intensity in the left pontine tegmentum (Fig. 1). The patient was treated with a course of prednisone, and the VIth nerve palsy resolved over 2 weeks.

Case 2

A 41-year-old white woman was in good health until she had a reaction to Motrin consisting of fever, headache, and a facial rash. When readministered, the drug led to a recurrence of the reaction with the additional symptom of left hand numbness. These symptoms resolved, and the patient was well until 4 months later, when she developed diplopia. Neurologic examination demonstrated a left VIth nerve palsy and hyperreflexia in the upper extremities. Additional findings included equi-}

cal Chaddocks signs, past pointing to the left, and decreased perception of vibratory sensation in the lower extremities. A CSF analysis was positive for the presence of oligoclonal bands (four bands) and markedly elevated IgG synthesis of +24.1 (normal range -5.0 to +5.0). An MRI revealed multiple areas of increased signal intensity in the white matter and with one focus of increased signal intensity in the left pontine tegmentum extending into the left basis pontis (Fig. 2). The VIth nerve palsy resolved slowly over a 10-month period.

Case 3

A 61-year-old was referred to the neuro-ophthalmology clinic for evaluation of diplopia, which had developed over several days. During a review of neurologic symptoms, the patient recalled that 3 years earlier, he had a transient diplopia lasting for several days along with progressive lower facial weakness of several years duration. In addition, the patient had experienced stiffness in the right lower extremity for many years. Neurologic examination demonstrated a left VIth nerve palsy, lower motor neuron distribution right facial weakness, paraparesis with weakness more prominent on the right, right ankle clonus and Babinski sign, and significant loss of vibratory sensation in the lower extremities. A CSF examination revealed the presence of oligoclonal bands (4 bands) and a mild elevation of IgG synthesis at
5.3 mg/day (normal range -5.0 to +5.0). A MRI scan demonstrated multiple areas of increased signal intensity in the periventricular white matter, cerebellum, and pontine tegmentum (Fig. 3). Resolution of the VI\textsuperscript{th} nerve palsy occurred over a 4-month period.

Case 4
A 37-year-old white woman was in excellent health until she awoke with diplopia. The symptom persisted for 1 week before she consulted an ophthalmologist. A left VI\textsuperscript{th} nerve palsy was documented. She had experienced an episode of transient paraesthesias and numbness in the right upper extremity and shoulder, as well as a separate episode in the left lower extremity in the past. Oligoclonal bands (5 bands) were demonstrated in the CSF. A MRI scan demonstrated multiple white matter areas of increased signal intensity in the cerebral hemispheres. No pontine abnormalities were detected. The patient was treated with oral prednisone, and the VI\textsuperscript{th} nerve palsy resolved over a 2-week period.

RESULTS
Three women and one man ranging in ages from 25 to 61 years had VI\textsuperscript{th} nerve palsy (Table 1). All patients were found to have abnormal cranial MRIs demonstrating white matter lesions in both cerebral hemispheres on T2 weighted images. Oligoclonal bands were present in the CSF of all patients at the time of diagnosis. The duration of the VI\textsuperscript{th} nerve dysfunction ranged from 2 weeks to 10 months. It is interesting that all four patients had a diplopia caused by a VI\textsuperscript{th} nerve deficit as a presenting symptom (Table 1), which led to further investigation and a diagnosis of MS. All patients had clinical findings in addition to the VI\textsuperscript{th} nerve palsy; however, signs and symptoms of ipsilateral brainstem injury—facial paresis, Horner’s syndrome, conjugate gaze paresis, deafness, loss of taste, and contralateral hemiparesis—were absent. None of the patients had evidence of an internuclear ophthalmoplegia. The patients subsequently experienced periods of relapse and remission and classified as definite MS (5).

A review of the MRIs revealed that patients 1, 2, and 3 had focal areas of increased signal intensity in the pons (Figs. 1, 2, and 3, respectively). Each of these patients had a white matter abnormality ipsilateral to the side of the palsy as shown by MRI. These focal areas of increased signal intensity involved the VI\textsuperscript{th} nerve nucleus (Fig. 1), the pontine tegmentum anterior to the nucleus (Fig. 2) or the VI\textsuperscript{th} nerve fasciculus (Fig. 3). In patient 2 the anterior portion of the pons on the opposite side was also abnormal (Fig. 2). Patients 1 and 3 had areas of increased signal in the cerebellum as well as in the pons. Only patient 4 had no evidence of an infratentorial abnormality by unenhanced MRI (Table 1).

DISCUSSION
Many recent studies have documented the sensitivity of the MRI for detection of lesions in MS patients (6–8). Abnormalities of the brainstem tend to correlate with clinical symptomatology and may be demonstrated in 15% of patients at the time of diagnosis (8,9). Previous case reports on two individuals suspected of having MS demonstrated pontine lesions on MRI correlating with bilateral gaze palsy. In addition, bilateral fascicular sixth cranial palsies have been documented as individual case reports (10,11).

The present study indicates that the anatomic site of a lesion producing an apparent VI\textsuperscript{th} nerve palsy in patients with MS can be identified by MRI in some cases. The MRI findings suggest that an acute VI\textsuperscript{th} nerve palsy may be produced by lesions in the tegmentum and/or the adjacent white matter in the basis pontis. The resultant VI\textsuperscript{th} nerve palsy
TABLE 1. Multiple sclerosis patients with VIth cranial nerve dysfunction

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Presenting symptom</th>
<th>Duration</th>
<th>OCB*</th>
<th>Cerebrum</th>
<th>Cerebellum</th>
<th>Pons</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24</td>
<td>F</td>
<td>Yes</td>
<td>2 weeks</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>41</td>
<td>F</td>
<td>Yes</td>
<td>10 months</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>M</td>
<td>Yes</td>
<td>3 months</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>37</td>
<td>F</td>
<td>Yes</td>
<td>2 weeks</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

OCB, oligoclonal bands; MRI, magnetic resonance imaging.


In these patients was secondary to demyelination of the fasciculus as it courses through the tegmentum or basis pontis.

One patient with an acute VIth nerve palsy had no evidence of involvement near the nucleus of the VIth nerve or its fascicle despite an obvious clinical deficit. We have observed a similar situation with definite MS patients presenting with acute onset of either internuclear ophthalmoplegia or IVth nerve palsy. In such cases, the patients with clinical deficits have no evidence of brainstem abnormalities by MRI, but there are obvious lesions distributed in the cerebral hemispheres. Since the unenhanced MRI is dependent on the presence of increased water content to demonstrate an abnormality, the negative result in these patients suggests that brainstem inflammation and demyelination may have been present in small lesions without enough of an increase in water content to be detected by unenhanced MRI. Thus, some acute lesions may have demyelination without increased water content, or they may be small and difficult or impossible to detect by unenhanced MRI utilizing inter-slice gaps as in patient 4. Time course studies in MS patients with acute onset of VIth nerve palsy would be of particular interest for evaluating the evolution of the brainstem lesions. Future investigation with axial images of reduced thickness without gaps and gadolinium enhancement, which detect defects in the blood brain barrier, will likely increase the sensitivity of MRI for detecting acute brainstem lesions in MS (12).
Evolution of Oculomotor Nerve Palsies

Hilda Capó, M.D., Floyd Warren, M.D., and Mark J. Kupersmith, M.D.

The management of patients with isolated oculomotor nerve palsies (OMPs) who have normal pupils and no other signs of neurological disease is a controversial issue. A more precise delineation of the clinical course of isolated OMPs may help to determine whether neuroradiologic evaluation is indicated in these cases. We studied 41 patients with isolated third cranial nerve palsies, emphasizing the times of progression and resolution of the oculomotor nerve dysfunction. The average interval from onset to development of maximal ophthalmoplegia failed to differentiate between a microvascular etiology (3.3 days) or posterior communicating artery aneurysm (3 days). Of the 28 patients with diabetic or idiopathic palsies, regardless of pupillary involvement, 68% had improvement of the oculomotor paresis within 4 weeks, 96% within 8 weeks, and 100% within 12 weeks of the onset of symptoms. Our study suggests that patients with pupil-sparing OMPs should be considered for extensive neuroradiologic evaluation only if there is deterioration or failure to improve within 4 to 8 weeks.

Key Words: Intracranial aneurysm—Oculomotor palsy—Third cranial nerve.

SUBJECTS AND METHODS

We reviewed the medical records of patients evaluated between 1982 and 1989 by the New York University Medical Center Neuro-Ophthalmology Service for acute isolated third nerve palsies. Only
patients with adequate history and follow-up were included. In order to assess only patients with an isolated OMP, patients with additional cranial neuropathies or systemic or neurologic symptoms at presentation were not included. Traumatic cases and those with evidence of SAH were also excluded. Particular attention was given to the pupillary status, presence of pain, the degree of involvement of the extraocular muscles (EOM), and the time course of evolution of the OMP.

Patients were grouped according to the degree of pupillary and EOM involvement (Table 1). Partial pupillary dysfunction was defined as ipsilateral pupil dilation of more than 1 mm or decreased reactivity in cases of equal pupillary size. External ophthalmoplegia was considered partial when the appropriate muscles were underacting but not fully paralyzed, or when some of the appropriate muscles were spared.

Cases were classified according to the etiology of the third nerve palsy. Idiopathic and diabetic palsies were grouped together on the presumption that both share an ischemic microvascular etiology and a benign course. Cases of intracavernous internal carotid artery (ICA) aneurysms and meningiomas of the cavernous sinus region were combined as compressive lesions of the cranial nerves in the cavernous sinus. All patients with pupillary involvement, except one, underwent CT or MRI and cerebral angiography to confirm that there was no intracranial aneurysm.

**RESULTS**

Forty-one patients met our criteria for inclusion. Twenty-eight of them (66%) had an idiopathic or diabetic (presumed microvascular) etiology, and 10 patients (26%) had angiogram-proven aneurysms (7 PCoA, 3 cavernous ICA). Two patients (5%) had a meningioma in the cavernous sinus area, and one (3%) had CNS lymphoma.

<table>
<thead>
<tr>
<th>TABLE 1. Degree of oculomotor nerve involvement</th>
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<tbody>
<tr>
<td>Diabetic or idiopathic</td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>NP, PO</td>
</tr>
<tr>
<td>NP, CO</td>
</tr>
<tr>
<td>PP, PO</td>
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<tr>
<td>PP, CO</td>
</tr>
<tr>
<td>CP, PO</td>
</tr>
<tr>
<td>CP, CO</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

CNS, central nervous system; NP, normal pupil; PP, partial pupil dysfunction; CP, complete pupil dysfunction; PO, partial external ophthalmoplegia; CO, complete external ophthalmoplegia.

**Idiopathic or Diabetic Etiology**

The group with idiopathic or diabetic etiologies included 12 women (43%) and 16 men (57%), with an average age of 67 years (range 25–89 years). Five patients had diabetes mellitus, 7 had high blood pressure, and 2 had both diseases (Table 2). The 14 patients without any known systemic disease had a negative 4- or 5-hour glucose tolerance test.

The pupil was spared in 21 patients (75%) and involved in 7 (25%). Two of the seven patients with pupillary involvement initially presented with pupillary sparing, but developed pupil paresis at days 11 and 14. Of those with pupillary involvement, three had complete iridoplegia and four had partial pupillary dysfunction; EOM dysfunction was complete in four patients and partial in three (Table 1). Six of the patients with pupillary involvement had a normal head CT or MRI and a normal cerebral angiogram of the ipsilateral ICA and vertebobasilar artery, which confirmed the absence of an aneurysm. The only patient who refused cerebral angiography had a normal MRI and spontaneous improvement of the paresis.

Of the 21 patients with pupillary sparing, 17 had partial and 4 had complete external ophthalmoplegia (Table 1). In two of these patients, only the superior division was involved. Because third nerve ischemia rarely spares the inferior division, these patients had a head and orbit CT or MRI, the results of which were normal.

Ipsilateral periorbital or retroorbital pain was present in 16 patients (61%) with a microvascular etiology. The pain preceded the onset of ophthalmoplegia in seven patients, was concurrent in eight, and appeared afterwards in two.

The time from the first symptoms to the development of maximal internal and external ophthalmoplegia is shown in Fig. 1. The mean time of progression was 3.3 days (SD ± 3.2). The improvement rate is shown in Fig. 2. Sixty-eight percent of the patients had improvement of the OMP within 4 weeks; 96%, within 8 weeks; and 100%, within 12 weeks of the onset of symptoms.

<table>
<thead>
<tr>
<th>TABLE 2. Distribution by etiology</th>
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<tbody>
<tr>
<td>Diabetic or idiopathic</td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>Total cases</td>
</tr>
<tr>
<td>Average age</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Pain</td>
</tr>
<tr>
<td>DM</td>
</tr>
<tr>
<td>HBP</td>
</tr>
<tr>
<td>DM and HBP</td>
</tr>
</tbody>
</table>

DM, diabetes mellitus; HBP, high blood pressure.
OCULOMOTOR PALSY

23

FIG. 1. Interval from first symptoms of oculomotor nerve palsy to maximal ophthalmoplegia.

Posterior Communicating Artery Aneurysms

Seven patients (18%), all with pupillary dysfunction at presentation, had angiogram-proven PCoA aneurysms ipsilateral to the OMP. There were five women and two men, with a mean age of 57 years (range 37-68 years). Two of the patients had high blood pressure, and none had diabetes mellitus (Table 2). Pain was present in five patients (71%) and preceded the onset of ophthalmoplegia in four. Pupil dysfunction was complete in four patients and partial in three. The external ophthalmoplegia was complete in four patients and partial in three (Table 1).

The course of progression is shown in Fig. 1. The difference in the mean time of progression between the microvascular (3.3 days) and the PCoA (3 days, SD ± 2.7) OMPs was not statistically significant by the Mann-Whitney test.

Cavernous Sinus Lesions

Three patients (8%) had angiogram-proven aneurysms of the intracavernous portion of the ICA, and two (7%) had a meningioma in the cavernous sinus area. Both conditions were grouped together as compressive lesions of the cranial nerves in the cavernous sinus. The three patients with intracavernous ICA aneurysms were women (25, 67, and 74 years old), and the two with meningiomas were men (55 and 70 years old). Three patients had periorbital pain ipsilateral to the lesion (two ICA aneurysms, one meningioma). The external ophthalmoplegia was partial in four and complete in one patient; three patients had internal ophthalmoplegia (Table 1). The two patients with pupillary sparing (one meningioma, one ICA aneurysm) had no improvement of the OMP by eight and nine weeks, when neuroradiologic studies were performed. The time course of progression was variable, ranging from 1 day to 3 years. One patient with a cavernous ICA aneurysm had spontaneous thrombosis of the aneurysm, with improvement of the pupil-involving OMP within 1 month and complete resolution within 4 months.

Lymphoma

One patient who initially presented with a partial internal and external OMP worsened over 1 month and developed paresis of the ipsilateral fourth and sixth cranial nerves. Magnetic resonance imaging and cerebral angiography performed at the time of presentation were normal, but the glucose tolerance test demonstrated a diabetic curve. A lumbar puncture, performed at 1 month, revealed lymphoma cells in the spinal fluid. A systemic evaluation did not show lymphoma outside of the central nervous system.

DISCUSSION

The recommendations for the evaluation of patients with a nontraumatic, isolated third cranial nerve palsy usually vary according to the degree of pupillary and EOM involvement. The question is: To what extent is a third nerve paresis a harbinger of a life-threatening condition, such as an intracranial aneurysm?

Intracavernous ICA aneurysms can occasionally cause an isolated OMP, but these differ from the PCoA and basilar artery aneurysms in that they carry only a minimal risk of producing a significant neurological deficit or death. Rupture of intracavernous ICA aneurysms usually results in a carotid-cavernous fistula without causing SAH. Only two cases of SAH caused by a ruptured intracavernous aneurysm have been reported (7,8). Consequently, emergency treatment in most cavernous carotid aneurysms is not recommended.

Approximately 86-100% of patients with OMPs caused by intradural aneurysms will have some degree of pupillary dysfunction at presentation (2,4,9-11) making it necessary to exclude an aneurysm in cases where the pupil is involved. It is
generally agreed that, because of the risk of a SAH from rupture of PCoA or basilar artery aneurysms, patients with partial or complete iridoplegia, irrespective of the degree of external ophthalmoplegia, should have neuroradiologic studies including cerebral angiography for patients older than 20 years of age. If the results of these studies are normal, a lumbar puncture should be performed to rule out a low-grade meningitis or lymphoma.

Patients with complete external ophthalmoplegia and sparing of the pupil are most likely to have suffered an ischemic event (3). A microvascular infarct of the extra-axial portion of the nerve with sparing of the peripheral pupilloconstrictor fibers has been identified in pathology specimens from diabetic OMPs, which explains the preservation of the pupillary function (12-14). Therefore, cerebral angiography is usually not initially recommended when the pupil is spared and the patient is 50 years of age or older and without SAH (3). Recently, Lustbader and Miller (5) reported a complete external ophthalmoplegia with pupillary sparing in a patient with a basilar artery aneurysm. This is the only case in the literature of an intracranial aneurysm with this presentation. The clinical course of this patient differed from that of our patients with microvascular disease in that there was no improvement 8 weeks after the onset of symptoms, while 96% of our patients had already improved by this time. We agree with previous recommendations (15) that patients with complete external third nerve palsies and sparing of the pupil do not require neuroradiologic studies except when the patient either deviates from the usual clinical course of an ischemic OMP or in younger patients in whom an ischemic process is therefore unlikely.

Trobe (3) recommends cerebral angiography for adults with an incomplete OMP and a normal pupil, particularly if the inferior division is spared. Although diabetic isolated palsies of the superior division of the third cranial nerve have been reported (16), these palsies are most commonly caused by compressive lesions, such as neoplasms and aneurysms of the ICA in the anterior cavernous sinus, where the nerve bifurcates (17) or less frequently, by basilar artery aneurysms (17,18). In patients with a superior division paresis of the oculomotor nerve, a high-resolution contrast CT scan or MRI is usually adequate to visualize the cavernous sinus and basilar artery areas and should be initially obtained in these patients (17).

There are very few cases in the literature of PCoA aneurysms causing incomplete OMPs with a normal pupil. Kissel et al. (4) and Oono et al. (20) have each reported one case of a PCoA aneurysm with a pupil-sparing partial third nerve palsy. Bartleson et al. (21) reported three patients who presented with an incomplete pupil-sparing OMP caused by unruptured intracranial aneurysms, one in the basilar artery and two in the ICA (presumably PCoA junction). None of these patients had improved 6 weeks after the onset of symptoms. Kissel et al. (4) reported four patients with PCoA aneurysms without SAH, who presented initially with pupil-sparing partial OMPs. However, one had an ipsilateral abducens palsy; two developed a complete iridoplegia within 5 days; and one, by 4 months. Pupil-sparing, partial OMP appears to be a rare presentation of intracranial aneurysms, but is common in idiopathic or diabetic OMP as observed in 61% of our patients with microvascular etiology (Table 1).

Since most of the patients with intracranial aneurysms initially have an abnormal pupil, or will develop pupillary involvement within several days of the ophthalmoplegesis (4,6), and 68% of the patients with idiopathic or diabetic OMPs will improve by 1 month and 96% by 2 months, it seems prudent to closely observe the patient with a pupillary-sparing third nerve paresis for 4 to 8 weeks before performing neuroradiographic studies, particularly cerebral angiography. Previous reports suggest that a CT scan MRI scan should be performed earlier in adults younger than 50 years of age and in those with an isolated superior branch paresis. It may be argued that 4 weeks is a long period of time, since Okawara (22) found that in cases of PCoA aneurysms the EOM involvement preceded the rupture of the aneurysm by an average of 29.6 days. It should be noted, however, that this average was based on only 6 cases, and no information was provided on the pupillary status, so this information may not apply to cases of pupil-sparing OMP.

It is unfortunate that the time of progression of the third nerve paresis is not helpful in distinguishing patients with an ischemic etiology from those with an aneurysm. We found that both groups worsened over an average of approximately 3 days.

In conclusion, patients with OMPs that involve the pupil (either initially or later) should have expedited noninvasive neuroimaging studies and cerebral angiography at the time of presentation. In patients with isolated complete or partial external ophthalmoplegia and normal pupils, the clinical course remains helpful in determining the extent of the neuroradiologic evaluation. Though one could argue that the miniscule risk of MR or CT
warrants that all patients be studied, our data suggests that only patients who fail to improve within 4 to 8 weeks must be scanned. According to previous reports, exceptions include patients with a superior division paresis in whom compressive lesions are common, and younger patients in whom an ischemic process is unlikely.

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Levator-Sparing Nuclear Oculomotor Palsy
Clinical and Magnetic Resonance Imaging Findings

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Two patients with diplopia presented with unilateral oculomotor palsy, defective elevation of the contralateral eye, and sparing of the levator palpebrae muscle. In each case, magnetic resonance imaging disclosed an infarction of the oculomotor nuclear complex in the mesencephalon. This clinical neuroradiological correlation is consistent with Warwick's scheme pertaining to the neuroanatomy of the oculomotor nuclear complex and demonstrates the utility of MRI in diagnosing ocular motility disorders of brainstem origin.

Key Words: Levator palpebrae muscle—Magnetic resonance imaging—Unilateral oculomotor palsy.

The oculomotor nucleus complex represents a specialized functional organization of axonal cell bodies located within the rostral midbrain at the level of the superior colliculus. Warwick's primate research provides the basis of the current understanding of the functional anatomy of the oculomotor nucleus (1). It is assumed that the oculomotor nuclear complex in nonhuman primates closely resembles that of man. However, only a limited number of cases in humans with clinicopathologic or clinicoradiologic verification of nuclear oculomotor palsies have been described in the literature. The following case reports support Warwick's conceptualization of the oculomotor nuclear complex in humans and are, to our knowledge, the first such cases in the English literature with clinical neuroradiologic correlation utilizing magnetic resonance imaging.

CASE STUDIES
Case 1
A 74-year-old man presented to a local emergency room with a history of sudden onset nausea, dizziness, and weakness followed 30 minutes later by unresponsiveness. His medical history was remarkable for hypertension, atherosclerotic vascular disease, noninsulin-dependent diabetes mellitus, and dementia. The patient had suffered an occipital infarction and had undergone right carotid endarterectomy 3 months prior to presentation.

An examination upon admission in September 1989 revealed that the patient was unresponsive, with a systemic blood pressure of 154/70 mm Hg. The left pupil was dilated, measuring 8 mm in diameter, and did not react to light. The right pupil reacted briskly to light. Oculocephalic reflexes of the left eye demonstrated normal abduction but a
complete adduction deficit. The right eye showed full horizontal motility. The patient had a flaccid right hemiplegia and a positive right Babinski reflex. Computed tomography (CT) of the head showed only an old occipital infarction.

The patient was placed on heparin anticoagulation therapy. He became responsive, and the hemiparesis resolved within several days. He was discharged on Coumadin with a diagnosis of a residual third nerve palsy. The Coumadin was subsequently discontinued, and daily aspirin therapy was begun for stroke prophylaxis. The patient was referred for evaluation of persistent diplopia.

A neuro-ophthalmologic examination in December 1990 demonstrated visual acuity of 20/25 OD and 20/30 OS. There were 40 prism diopters (PD) of left exotropia with 12 PD of left hypertropia in the primary position. Testing of ocular ductions showed deficient adduction and depression of the left eye. Elevation was decreased bilaterally, more notably in the right eye (Fig. 1). The pupils measured 3.0 mm on the right and 3.5 mm on the left. The right pupil reacted briskly to light; the left reacted sluggishly. No afferent defect was present.

An external examination revealed no blepharoptosis. Magnetic resonance imaging (MRI) with gadolinium ethylenediaminetetraacetate (EDTA) enhancement disclosed a lesion involving the left oculomotor nucleus in the rostral brainstem (Fig. 2). Careful review of the MRI with a neuroradiologist revealed no rostral or caudal extension of the localized midbrain lesion.

Case 2

A 49-year-old man presented to a local emergency room in November 1988 with complaints of dizziness, headache, and ataxia, followed 4 hours later by onset of binocular vertical diplopia. There was no associated loss of consciousness. His medical history was remarkable for poorly controlled systemic hypertension.

Systemic blood pressure upon admission was 220/138 mm Hg. Computed tomography of the head demonstrated an intracranial hemorrhage in the right basal ganglia with possible brainstem extension. Cerebral angiography revealed no aneurysm. The patient gradually improved in the hos-
FIG. 2. Magnetic resonance imaging with gadolinium EDTA enhancement demonstrates a focal lesion involving the left oculomotor nucleus.

FIG. 3. T2-weighted magnetic resonance imagery shows a focal lesion at the level of the right oculomotor nucleus complex.

pital. His blood pressure was initially managed with intravenous nipride followed by oral procardin, hydrochlorothiazide, and capoten. The patient was referred for evaluation of persistent diplopia.

In April 1991, a neuro-ophthalmologic examination revealed a visual acuity of 20/25 OD and 20/20 OS. There were 25 prism diopters of right exotropia and 45 prism diopters of right hypertropia in the primary position. The right eye showed poor adduction and depression with a mild decrease in elevation. Ductions of the left eye were full except for deficient elevation. The pupils measured 4 mm on the right and 2 mm on the left. Pupillary light reaction was sluggish OD and brisk OS. No afferent pupillary defect was present. There was no blepharoptosis. The remainder of the ocular examination was normal. T2-weighted MRI demonstrated a lesion involving the right oculomotor nucleus complex consistent with a previous hemorrhagic infarction (Fig. 3). No rostral or caudal extension of the lesion was noted.

DISCUSSION

Since the 1800s, many researchers have speculated on the functional organization of the oculomotor nucleus. However, Warwick’s treatise is widely considered to be the classic work on this subject (1). Warwick examined primate oculomotor nuclei for evidence of retrograde degeneration after extirpation of different oculomotor-innervated extraocular muscles. Results demonstrated that within the oculomotor nucleus complex, the inferior rectus, inferior oblique, medial rectus, superior rectus, and levator palpebrae muscles are each subserved by a specific compact group of cell bodies in the form of a subnucleus. These subnuclei exist as discrete narrow columns of cell bodies with a rostrocaudal and dorsoventral orientation within the brainstem. This functional organization of the oculomotor nucleus in nonhuman primates has been confirmed by more recent investigations (2,3). These studies involved examination of the oculomotor subnuclei for the presence of horseradish peroxidase from retrograde transport after injection of the marker into the various oculomotor-innervated extraocular muscles.

Studies demonstrate that innervation of the extraocular muscles supplied by the oculomotor subnuclei is ipsilateral except for the superior rectus and levator palpebrae muscles. Both levator palpebrae muscles are subserved by a single, centrally located subnucleus known as the central caudal nucleus. The superior rectus muscle receives innervation from a contralaterally located subnucleus. Because of this unique pattern of innervation, a unilateral oculomotor nucleus lesion causes bilateral eye movement dysfunction. Similarly, blepharoptosis resulting from a lesion of the oculomotor nucleus is always bilateral (4).
The presence in humans of a central caudal nucleus supplying both levator palpebrae muscles is supported by clinicopathologic and clinicoradiologic correlation. Because of its location at the far caudal and dorsal extent of the oculomotor nuclear complex, selective involvement of the levator subnucleus is possible, leading to isolated bilateral ptosis (5,6). More commonly, bilateral ptosis occurs in combination with an oculomotor paralysis (6-13). Rarely, a nuclear oculomotor nerve paralysis can occur without ptosis by sparing of the levator subnucleus (14,15). This was the case in both of our patients.

Nerve fibers originating in the contralateral superior rectus subnucleus have been shown to pass through the ipsilateral oculomotor nuclear complex to exit in the nerve fascicle (16). Thus, a nuclear third nerve lesion is expected to cause bilateral supraduction deficits in addition to ipsilateral dysfunction of the medial rectus, inferior rectus, and inferior oblique muscles. Such bilateralparesthesia of elevation has been termed a pseudo-Parinaud's syndrome (17). There are very few case reports to support Warwick's concept of crossed innervation of the superior rectus in humans (8,9,13,15,18-20).

Our two cases with clinical radiologic correlation by MRI provide further evidence that Warwick's scheme can be applied to humans. Clinically, the presence of ipsilateral exotropia and contralateral hypotropia is particularly revealing of a nuclear third nerve palsy in both cases and highlights the contralateral innervation pattern of the superior rectus subnucleus (17). It is interesting that in both patients, the central caudal nucleus is spared because of its unique and relatively isolated location within the oculomotor nucleus complex. Magnetic resonance imaging demonstrates the lesions within the mesencephalon, involving the oculomotor nucleus complex. Careful review of the scans with a neuroradiologist confirms the localized nature of these lesions with no extension in adjacent sections taken rostrally or caudally.

The presentation of patient 1 initially pointed to a lesion of the left oculomotor fascicle (21), but the patient was left ultimately with a nuclear third nerve palsy. Upon admission, a Weber's syndrome was diagnosed, consisting of a pupil involving oculomotor palsy and contralateral hemiplegia. Initial complaints of dizziness presumably resulted from involvement of the red nucleus or cerebellum. Ischemia to the rostral medial reticular formation may account for the somnolence and decreased responsiveness. The patient's rostral brainstem stroke was most likely caused by occlusion of the distal basilar artery and its small penetrating branches that supply the mesencephalon on the left side. Such occlusion occurs most frequently as a result of embolic disease (22). There was reversible ischemia to some affected areas of the mesencephalon, including the oculomotor nerve fascicle, but the infarction of the left oculomotor nucleus complex was permanent. Presumably, embolic occlusion of the proximal portion of the distal basilar artery and its penetrating branches was transient and reversible, making the patient's hemiparesis and somnolence temporary. Propagation of the embolus however, caused permanent occlusion of the distal extent of a paramedian penetrating artery with terminal arborizations around the left oculomotor nuclear complex.

Patient 2 suffered a hemorrhagic infarction of the oculomotor nucleus complex. A mesencephalic hematoma resulting in nuclear oculomotor paralysis has been reported only once in the literature (20). The oculomotor palsy in that patient improved with resolution of the midbrain hematoma over 1 week. Our patient suffered a permanent infarction of the oculomotor nerve nucleus.

The Edinger-Westphal subnuclei are located dorsal and rostral to the motor subunits of the oculomotor nucleus complex. In Warwick's scheme, these subnuclei are connected across the midline. As a result, pupil involvement might be expected to be bilateral if associated with a nuclear third nerve palsy. Nevertheless, ipsilateral pupillary abnormalities can occur in oculomotor nucleus injury (14,15). This was the case in both of our patients. The ipsilateral pupils were slightly larger and sluggishly reactive to light compared to the contralateral side. Presumably, the midline connection of the Edinger-Westphal subnuclei was not involved by the ischemic injury.

The cases presented are the first known reports in the English literature of nuclear third nerve palsy with clinical and neuroradiologic correlation by MRI. One case has been reported in the French literature (23). Clinical radiologic correlations of brainstem oculomotor fascicular lesions by MRI (24-26) or CT (27,28) have been reported. Magnetic resonance imaging of the posterior fossa is clearly superior to CT scan and is particularly useful in the neuro-ophthalmological evaluation of oculomotor abnormalities of brainstem origin (26,29).

In summary, these case reports help to verify Warwick's concept of crossed innervation of the superior rectus muscle in man. Each patient's unilateral oculomotor nuclear complex infarction caused bilateral supraduction deficits. In both cases, ptosis was absent from sparing of the centrally located levator subnucleus. The infarctions
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Esthesioneuroblastoma Presenting as Sudden Unilateral Blindness
Histopathologic Confirmation of Optic Nerve Demyelination

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We report here a case of esthesioneuroblastoma an 11-year-old girl presenting as acute loss of vision with minimal evidence of orbital, nasal, or paranasal sinus disease, a rare presenting symptom for this tumor. The initial diagnosis was postviral optic neuritis, a pattern of presentation not previously reported. When vision failed to improve, magnetic resonance imaging revealed a lesion in the posterior ethmoid and sphenoid sinuses. After a biopsy, the tumor was excised through the cranium and paranasal sinuses. A mass completely surrounding the optic nerve without invasion was found. Histochemical staining suggested demyelination secondary to compression, confirming the clinical impression of optic neuritis. Anti-Leu 7 monoclonal antibody is useful in characterizing of this tumor, since other immunohistochemical stains can be misleading. Radiation and chemotherapy were given after the tumor was removed. Two years later, the patient has had neither recurrence nor complications.

Key Words: Anti-Leu 7 monoclonal antibody—esthesioneuroblastoma—Postviral optic neuritis.

Esthesioneuroblastoma is a neuroectodermal tumor arising from the olfactory mucosa, frequently involving the eye and orbit. This case is unique because its clinical presentation suggested acute demyelination of the optic nerve, and this clinical impression was histologically confirmed when the tumor was found to surround, but not to invade, a demyelinated optic nerve.

CASE REPORT

The patient was an 11-year-old girl who was in good health until she experienced a rapidly progressive loss of vision in the left eye. Three days before the vision loss, she had developed "the flu," conventionally associated with headaches, ocular tenderness, and blurred vision. Over a 24-hour period, the visual acuity of the left eye decreased to the point at which there was no light perception. The visual acuity of the unaffected right eye was 20/20. There was a left afferent pupillary defect. The anterior segments of both eyes were normal. Both optic discs were well-demarcated with symmetric cup/disc ratios of 0.4. The maculas appeared normal bilaterally. Extraocular movements were normal. The visual field of the right eye was normal. No other physical or neurologic abnormalities were found.

The initial working diagnosis was a probable case of postviral optic neuritis of the left eye. Laboratory results indicated a white blood count of 6,500 with normal differential and a normal erythrocyte sedimentation rate.

The patient was observed over a 3-week period,
and when the vision failed to improve, imaging studies were performed. A computed tomography (CT) scan showed destruction of the body of the sphenoid bone posterosuperiorly, including the margins of the left optic canal. In addition, destruction of the planum sphenoidale on the left side was noted, associated with a broad-based thin intracranial mass. There appeared to be erosion of the lamina papyracea and minimal extension of the mass into the posterior orbit and ethmoid sinuses. The anterior ethmoid cells were not involved. The intracranial portion of the tumor was thought to be extradural and almost certainly extracerebral. The region of the cribriform plate was not involved (Fig. 1).

Magnetic resonance imaging (MRI) revealed an abnormal signal within the entire left sphenoid sinus (Fig. 2). There was slight expansion of the superior and lateral walls of the sphenoid and posterior ethmoid sinuses. The left optic nerve appeared slightly compromised by lateral expansion of the sinus into the optic canal and medial wall of the left orbit. The intracranial portion of the optic nerves and chiasm were completely normal.

When biopsied, the sphenoid sinus mass was found to be an esthesioneuroblastoma. Because of the circumferential involvement of the optic nerve and its very posterior location, an en bloc resection attempting to achieve tumor-free margins would have had to include such vital structures as the pituitary gland and was therefore not considered.

Considering the age of the patient, lack of metastases, and noninvolvement of the other optic nerve, we decided to perform gross total surgical excision as the primary procedure and to utilize radiation and chemotherapy postoperatively.

The cranial vault was entered through a bifrontal approach. The soft tissue was easily identified in the region of the left optic nerve, displacing but not penetrating the overlying dura. The tumor extended from the midline to the limbus sphenoidale and from the anterior clinoids to the left cavernous sinus. The entire left anterior clinoid and optic canal were totally excised. Because of its proximity to vital structures, the remaining tumor was removed piecemeal. All of the visible tumor was removed from the ethmoid and sphenoid sinuses.

Postoperatively, the consensual pupillary light reflex and ocular motility remained normal. A course of radiation therapy, totaling 5,075 cGy, was given to the involved region. Nine courses of chemotherapy (vincristine and cytoxan) were given. At the most recent examination, 29 months postoperatively, there has neither been evidence of recurrence of tumor nor delayed ophthalmologic complications. The patient’s endocrine status is apparently normal.

HISTOPATHOLOGICAL FINDINGS

Two portions of optic nerve and multiple irregular fragments of bone were evaluated. At one end of the larger optic nerve segment, there was a cuff of tissue 13 mm in diameter. The optic nerve parenchyma had undergone mild diffuse swelling and degeneration associated with a mild degree of gliosis. There was no evidence of direct tumor involvement of the optic nerve. Luxol-fast blue stained specimens confirmed demyelination of axons, and Bielschowsky silver stain confirmed neuroaxonal degeneration (Figs. 3 and 4).

The tumor adjacent to the optic nerve was characterized by sheets of small cells with prominent nuclei and eosinophilic cytoplasm. The cell margins were indistinct. In some areas, the tumor was divided by fibrous septae. Neoplastic cells infiltrated bone and were present immediately beneath respiratory mucosa. There was no histologic evidence of differentiation. There was no fibrillary background nor rosette formation. Immunoperoxidase stains for chromogranin, Synaptophysin, actin, desmin, and neurofilaments were negative. There was faint positivity for Leu 7 and neuron-specific enolase (Fig. 5). The ultrastructure of the tumor cells was characterized by many cell processes, some of which contained membrane-
FIG. 2. Axial (A) and coronal (B) MR images without contrast show a mass filling the entire left sphenoid sinus and extending into the left posterior ethmoid sinus.

bound, electron-dense material, consistent with neurosecretory granules (Fig. 6). Microtubules could be observed in several cell processes. The cytoplasm also contained mitochondria, focally dilated Golgi apparatus, and numerous cytoplasmic intermediate filaments. The immunohistochemical and ultrastructural features of neuroblastic differentiation were the basis for the diagnosis of esthesioneuroblastoma.

DISCUSSION

Esthesioneuroblastoma is a malignant, slow growing, neurogenic neoplasm originating in the olfactory mucosa of the upper nasal cavity (1). The neoplasm originates from cells derived from the neural crest (2). In the nasal cavity, the usual primary sites include the superior nasal cavity or nasal septum, the turbinates, or the cribriform plate.

FIG. 3. Luxol-fast blue stain demonstrates demyelination of fibers in the periphery of the nerve. Between arrows ×115.
and fovea ethmoidalis (2). This neoplasm may also arise as a primary tumor within the paranasal sinuses or intracranially (3).

In a series of 39 cases, Jackson found a preponderance of women (23 in 39) ranging in age from 1 to 65 years in whom the tumor most commonly occurred in the second decade of life (2). In contrast to neuroblastomas in other anatomic sites, olfactory tumors primarily affect adults. This may be related to the fact that the olfactory neuroepithelium, unlike other central neuroectodermal tissue, exhibits continual cellular turnover (4). In another series of 48 patients with malignant tumors of the nasal cavity, the ethmoid, and the sphenoid sinuses, eight tumors were found to be esthesioneuroblastoma (5).

**FIG. 4.** Bielschowsky silver stain shows neuraxonal degeneration (arrow) in the area corresponding to right arrow of Fig. 3 that is demyelinated; some residual axons are seen in the lower half of the figure. ×400.

**FIG. 5.** Immunoperoxidase stains show faint cytoplasmic positivity for neuron-specific enolase (left) and membrane-based, for leu 7 (right).
The neoplasm is noted for its variability of clinical presentation (6). Because esthesioneuroblastoma is usually derived from the lining of nasal cavities and paranasal sinuses, the presenting symptoms often include nasal obstruction and congestion, epistaxis, facial numbness and swelling, diplopia, ocular pain, proptosis, or headaches (2). The tumor may present as an inflammatory nasal polyp (7).

In a Mayo Clinic series, 28 of 38 cases were associated with ophthalmic signs or symptoms at some time during the course of the disease. Of the 28 cases, ophthalmic signs were manifested when the neoplasm was initially diagnosed in 20 cases. Signs and symptoms included peri orbital pain, excessive tearing, eyelid edema, proptosis, globe injection, and ptosis. Five of these patients presented with coexisting ophthalmic, but not visual, complaints (8). Patients may rarely present with visual abnormalities. Two such cases have been reported: in one, intracranial extension from a sphenoid or ethmoid sinus produced purulent meningitis associated with blindness (9); the other patient developed loss of vision 6 months after developing anosmia (10).

The reported incidence and extent of metastasis of esthesioneuroblastoma has been variable (11). The sites of distant metastasis include cervical lymph nodes, bones, soft tissue, and brain (7,12,13). Tumor cells may be distributed by the cerebrospinal fluid to such remote sites as the posterior fossa (13) and even the cauda equina (6). Metastasis may be delayed as in the case reported by Rodas (11) in which metastatic disease developed in the right parietal cortex and meninges 5 years after surgical and radiotherapeutic treatment of a primary lesion. No convincing relationship has been shown between histologic appearance and behavior (2).

Computed tomography most often shows esthesioneuroblastoma to be a soft tissue mass that adheres to the cribiform plate, usually with bone lysis (1). Two cases have been reported in which hyperostosis was present (1). Magnetic resonance imaging with multislice T1-weighted images is useful for showing tumor extension into paranasal sinuses. Increasing degrees of T2-weighting allow the tumor to be differentiated from fluid retention secondary to compression of the normal sinus orifices (14). Scintigraphy has also been used to identify the tumor (15).

Light microscopy shows that cytologic features include uniform, small, round-to-oval cells with coarsely granular chromatin, multiple small nucleoli, prominent nuclear membranes, and scant cytoplasm (12). A prominent fibrillary background is often present. The neuroblasts are occasionally ar-
ranged into both rosettes of the Homer-Wright type and pseudorosettes although the tumor cells may show axon production (16), differentiation into mature ganglion cells does not take place. The cytologic appearance of tumor cells in cerebrospinal fluid may be misinterpreted as anaplastic carcinoma, rhabdomyosarcoma, melanoma, and non-Hodgkins lymphoma (6).

Ultrastructural characteristics include dense core secretory granules in the cytoplasm and cell processes (12,17). The dendritic processes contain microtubuli and filaments as well as secretory granules of 1800A. The production of dense core granules is the most characteristic ultrastructural feature (16).

Anti-Leu 7 monoclonal antibody recognizes a protein originally identified in natural-killer cells; however, this protein is also present in most neoplasms of neuroectodermal origin and can be helpful as part of a battery of immunostains (18) in the differential diagnosis of these tumors. It is important to use a carefully designed battery of immunostains in the differential diagnosis of olfactory neuroblastomas because reactivity for other markers, such as leukocyte common antigen, S-100 protein, and HMB-45, or desmin and actin would identify a small cell tumor of this anatomic region as a lymphoma, small cell melanoma, or rhabdomyosarcoma, respectively.

Esthesioneuroblastoma is clearly aggressive and needs to be treated accordingly (6). Many centers now consider chemotherapy to be the treatment of choice, either with or without surgical intervention (19). Vincristine and cytoxan sometimes supplemented by doxorubicin is the usual regimen. Early lesions without signs of metastases may be treated surgically in the hope of achieving a definite cure. Metastatic lesions are usually treated by chemotherapy alone. In a series of 26 cases reported by Willen (7), there was a 17.5% survival for nonaggressively treated cases compared to 82% with more aggressive multi-agent chemotherapy. High-dose chemotherapy and autologous bone marrow transplantation was used in 26 patients to treat advanced disease (20).

Preoperative and postoperative radiation therapy has been used routinely with good results. Preoperative treatment has not affected postoperative healing (21). In a recent study, it was found that radiation therapy is complicated by blindness in 33% of cases (5). One study showed that long-term survival could be linked to orbital or cervical lymph node involvement on initial presentation (22). The patient described in this article appears to follow that trend, doing well 2 years after surgery without signs of recurrence.

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Herpes Zoster Ophthalmicus
Anterior Ischemic Optic Neuropathy and Acyclovir

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A healthy 56-year-old man developed left-sided herpes zoster ophthalmicus, accompanied initially by ipsilateral anterior uveitis and increased intraocular pressure. Although he was treated in the subacute phase (5 days after skin eruption) with adequate oral doses of acyclovir for 10 days, the condition was later complicated by a left sectorial anterior ischemic optic neuropathy. The pathogenesis of this rare complication is discussed in this article.

Key Words: Acyclovir—Anterior ischemic optic neuropathy—Herpes zoster ophthalmicus.

CASE REPORT

An otherwise healthy 56-year-old man presented with a 7-day history of left ocular pain. Five days before his initial visit, red skin lesions appeared around the left eyebrow. He reported having had an attack of right HZO a few years ago without complications.

An examination revealed crusted skin lesions in the dermatome of the ophthalmic division of the left trigeminal nerve. Vision was 20/15 in both eyes. An examination of the right eye was unremarkable, but the left eye showed keratic precipitates, anterior uveitis (2+ cells) with intraocular pressure increased to 32 mmHg. Despite the presence of vesicles for more than 3 days, oral ACV 5×800 mg/day for 10 days was started, and local treat-
ment included ACV ointment 5×/day, scopolamine 0.25% 3×/day, and timolol 0.5% 2×/day.

Twenty-seven days later (17 days after treatment cessation), the patient experienced a sudden and painless loss of vision in his left eye. Vision decreased to 20/200, and the anterior segment was unremarkable, with a clear anterior chamber and intraocular pressure of 14 mmHg. A fundus examination revealed prominent optic disc edema with capillary dilation and an inferior splinter hemorrhage (Fig. 1). Fluorescein angiography was performed and showed early temporal superior hypofluorescence (Fig. 2, between arrows) with late diffuse staining, compatible with a sectorial AION. Goldmann perimetry (Fig. 3) showed an absolute visual field loss corresponding to the sector of disc ischemia. Ocular motility was normal. An examination of the right eye was unremarkable with a visual acuity of 20/15.

An extensive medical and neurologic examination failed to reveal any abnormality. The patient, a nonsmoker, showed no evidence of cardiovascular disorder. Arterial blood pressure was 125/80 mmHg. A cerebral computed tomography (CT) scan was normal. Neck and transcranial Doppler studies failed to show any arterial stenosis, and flow in the ophthalmic artery was normal on both sides. Blood examination showed erythrocyte sedimentation rate, 7 mm/h; hemoglobin, 156 g/l; hematocrit, 46%; platelets, 275 g/l; leukocytes, 10.1 g/l (neutrophils 72%, lymphocytes 23%, monocytes 5%); negative human immunodeficiency virus (HIV); glucose, 5.23 mmol/l; total plasma proteins 74 g/l. Cerebrospinal fluid contained slightly raised protein (635 mg/l; normal: <410 mg/l), which is a frequent finding in HZO (3,18).

Oral prednisone was started at 1 mg/kg/day and then tapered over 1 month. There was gradual reabsorption of the disc edema with temporal superior sectorial optic nerve atrophy. Visual acuity did not improve, and the visual field loss remained unchanged.
DISCUSSION

Herpes zoster ophthalmicus is caused by the reactivation of the varicella-zoster virus (VZV), which has remained latent in the Gasserian ganglion since the patient's primary infection. The reactivation of VZV is associated with a depression of the cellular-mediated immunity (21). Such an immunological depression is more common in elderly patients, as assessed by the lymphocyte-transformation test or by the skin test reactivity (21,22). Recurrences of HZO are frequent in immunocompromised hosts, but can surface in otherwise healthy patients. Hope-Simpson reported the frequency of a second attack of herpes zoster to be as common in patients with a previous episode of zoster as first attacks were in the general population (9 recurrences in 192 patients with previous zoster; 192 cases of zoster in 3,500 patients (23)).

Optic neuropathies are rare complications of HZO, probably occurring in less than 1% of all HZO cases (9,11-13,16,17). Whether anterior or posterior, the evolution and prognosis of VZV-induced optic neuropathies is unpredictable. Some patients have good visual recovery, and others experience poor or no visual improvement with or without treatment, depending on the severity and the type of tissue injury— ischemic or demyelinating (24).

A sudden, painless visual loss occurred 32 days after the onset of HZO in our patient despite a 10-day course of ACV at an adequate dosage but started late (5 days after skin eruption). The clinical presentation as well as the results of fluorescein angiography were typical of AION, possibly caused by either a thrombosis or an arteritis involving the short posterior ciliary arteries.

Ipsilateral cerebral ischemia is a well-recognized complication of HZO (25) and was found to appear at an average of 31 days following the onset of HZO in a review of 36 patients (26). Pathology data on lethal cases of HZO complicated by contralateral hemiplegia revealed segmental granulomatous angiitis (27,28). In these patients, VZV antigens were found within the media of ipsilateral cerebral vessels innervated by the trigeminal nerve, suggesting an immunological process involving the formation of tissular immune complexes.

Recent ocular pathology studies of HZO are lacking because of the generally good prognosis that has developed with the advent of acyclovir treatment (19). In 1968, Naumann et al. reported on pathology data from 21 eyes of HZO patients (29). These eyes were enucleated 7 days to 8 years after the onset of HZO because of pain, phthisis bulbi, or corneal ulceration. Posterior ciliary perineural and intraneural as well as vascular and perivascular lymphocytic infiltration was a prominent feature (18 of 21 cases) and was frequently found to be segmental. It is interesting that the eye of a 71-year-old woman, enucleated 5 weeks after the onset of HZO, showed a posterior ciliary granulomatous arteritis and a granulomatous choroiditis, features indeed very similar to HZO-related cerebral vasculitis. The fact that perineural and perivascular inflammation was less pronounced in the early enucleated eye (7 days after HZO onset) than in 3 eyes enucleated later (5, 6, and 12 weeks after HZO onset) suggests that immunological processes are involved in the pathogenesis of HZO. These pathological reports support the idea that AION in our case could be due to segmental posterior ciliary granulomatous arteritis. Reactivation of viral replication occurring at the end of ACV therapy is mostly unlikely in our patient, as this is the case only in severely immunocompromised patients, thus favoring the hypothesis of an immune-induced arteritis.

Acyclovir is an antiviral drug that is helpful in the acute phase of viral dissemination when direct viral invasion and replication occur (19). However, ACV is probably unable to influence secondary immunological processes. Treatment of HZO with a high dose of oral ACV (5 x 600-800 mg/day for at least 7 days) when given within 3 days of the cutaneous eruption drastically reduces the rate of severe ocular complications (19,20). Such treatment does not block the antibody titer rise against varicella-zoster virus (30). We recently showed that when given late, ACV does not reduce the rate of HZO-related ocular complications (31). For our patient, delayed ACV therapy did not prevent a secondary complication, as AION appeared 32 days after the onset of HZO, the same average time at which other cerebral complications were noted to appear (26).

Acyclovir has only been recently introduced, and we are aware of only two other reports of HZO-related optic neuropathies treated with ACV, both in HIV-positive patients (32,33). These patients had extensive ocular involvement (uveitis, vitritis, retinitis, and optic neuropathy) probably as a result of massive viral invasion. Optic nerve involvement occurred in the acute infectious phase in both patients and was ascribed to direct viral involvement. There was a favorable outcome in one case with ACV therapy alone (33).

In conclusion, because the type of late complication of HZO as seen in our patient is thought to
be immunological in nature, the recommended classical therapy is high-dose corticosteroids. The best prophylaxis, however, for severe HZO-related complications is ACV therapy given early and in an adequate dose.

REFERENCES

Pain Upon Eye Movement Following Digoxin Absorption

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A patient who had received digoxin for 6 months experienced glare and ocular pain induced by eye movement. The symptoms lasted for 2 days and disappeared within hours after the treatment was discontinued. Four months later, digoxin was readministered. After 2 days, the symptoms reappeared but disappeared again within hours of stopping treatment. The origin of the pain is uncertain, although mechanisms related to optic nerve or ocular muscle involvement should be considered. Digoxin toxicity should be included in the differential diagnosis of pain evoked by ocular movements.

Key Words: Digoxin—Glare.

Cardiac glycosides have been known for decades to induce toxic changes in the eyes and vision. Common side effects include glare, disturbance of color vision, and flickering of light (1–4). Temporary reduction in visual acuity is less common. Diplopia and ptosis have occasionally been mentioned in association with digitalis treatment, but these conditions may have been coincidental (1–5). We recently examined a patient with a history of repeated episodes of glare and ocular pain when moving the eyes. The symptoms occurred following digoxin intake and immediately resolved upon discontinuation of the treatment. Pain induced by eye movements has apparently not been reported in association with cardiac glycoside intoxication.

CASE REPORT

A 32-year-old woman suffering from truncus arteriosus communis type IV according to the classification of Collett and Edwards (6,7) was treated from the age of 8 to 16 with digoxin 0.25 mg four times daily. When she was 25 years old, weighing 56 kg, she received digoxin 0.25 mg daily because of heart failure. After 6 months of treatment, she began to experience deep orbital pain on both sides when moving the eyes in association with a glare phenomenon. The symptoms lasted 48 hours. Treatment was then discontinued, and less than 1 day later, all symptoms had disappeared. Sixteen weeks later, digoxin 0.25 twice daily was prescribed because of a recurrence of heart failure. After 2 days of treatment, the patient experienced dazzling and orbital pain on moving the eyes. Treatment was immediately interrupted, and the ocular symptoms disappeared within hours. No ophthalmological examination was performed during these events, nor were serum digoxin levels determined.
At the age of 32 at the request of the patient, who now is a physician, an attempt was made to explain these symptoms by administering digoxin 0.25 mg twice daily. Her body weight was still 56 kg. An ophthalmological evaluation performed before treatment showed 20/20 best corrected visual acuity in both eyes, normal fundus and ocular pressure, and full visual fields when evaluated by means of Goldmann kinetic perimetry. Pattern-VER and visual contrast sensitivity (assessed by Nicolet CS 2000) were within the normal range.

Three and four days after starting treatment, a reassessment of visual function showed reduced contrast sensitivity values. The patient declined electroretinography. Treatment was stopped, and tests given 1 week later showed that contrast sensitivity had returned to normal. At no stage of the therapeutic trial did the patient demonstrate any significant change in visual acuity, visual fields, pattern-VER, or fundus appearance. She did not experience color hallucinations, glare, or ocular pain. Serum digoxin level on the third day was found to be 1.58 mmol/l. Serum sodium and potassium levels were within the normal range.

DISCUSSION

This patient twice experienced dazzling and pain induced by eye movement during digoxin treatment. The ocular symptoms ended hours after therapy was discontinued. Despite the fact that these symptoms did not recur after a third therapeutic trial, this history strongly suggests a causal relationship between digoxin intake and the reported symptoms.

Dazzling is a common complaint of patients taking cardiac glycosides and has been noted either before, or in association with, a reduction in visual acuity (4). In affected patients, an alteration in visual function is generally attributed to changes in receptor cells of the retina (5,8,9). Involvement of the optic nerve in digoxin intoxication has also been suggested (1,2), but we cannot be certain that this actually occurs. It has been argued that absence of disc pallor, an alteration in electroretinography in patients receiving digoxin, and higher digoxin levels in the retina than in the optic nerve in guinea pigs receiving digoxin (8,9) support the existence of retinal rather than optic nerve involvement in visual disturbances caused by cardiac glycosides.

The origin of our patient's ocular pain induced by eye movement, is uncertain. Two hypotheses may be considered. First, considering that the patient showed changes in visual function and that pain on eye movement occurs with retrobulbar neuropathy (10) it is possible that the pain was related to optic nerve involvement. This, however, seems unlikely. While pain on eye movement is typically associated with retrobulbar neuritis (10), it has apparently not been reported in optic neuropathy from toxic causes. It is also conceivable that ocular pain resulted from extraocular muscle involvement (11), but few cases of ocular muscle changes caused by cardiac glycoside toxicity have been described. There have been two reports of ptosis and diplopia that occurred in association with the intake of cardiac glycosides (12,13). In these cases, however, ophthalmoplegia was probably neurogenic rather than myogenic in origin. Moreover, these patients did not report pain on eye movement. We are not aware of any reports of myalgia or myositis occurring in conjunction with treatment with cardiac glycosides. Digoxin intake may cause ocular pain on moving the eyes and should be considered in the differential diagnosis of this condition.

REFERENCES

Orbital Hydatid Cyst
Report of a Case Followed by Serial Computed Tomography

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A case of an orbital hydatid cyst which showed recurrence and regressed with antihelminthic therapy is described.

Key Words: Orbital cyst—Hydatid cyst—Echinococcus granulosus—Computed tomography.

Orbital hydatid cyst is very rare, while nonorbital forms constitute a still frequently encountered disease in Turkey (1-4). It has been stated that only 1% of all hydatid cysts are localized in the orbit (5). In 1982, two children with orbital hydatid disease were reported from our clinic (2). In this article, we report an additional case in whom we observed recurrence of the disease and in whom antihelminthic therapy caused complete clinical and radiological regression on serial scans.

CASE REPORT

This 5-year-old boy was admitted to our clinic on March 28, 1987, with a progressive left-sided exophthalmos that had started 9 months previously. From his history, we learned that his family were farmers and owned three sheep dogs.

General physical examination on admission was unremarkable. On routine chest radiograph examination, two well-circumscribed lesions, 1.5 cm in diameter, were observed on the right lung. Neuroophthalmological examination showed left-sided exophthalmos of 7 mm and papilledema. Visual acuity was 20/20 in the right eye, and 20/30 in the left eye. The left eyeball was pushed downward, outward, and forward. Upward, medial, and lateral ocular movements were limited on the left. The eyeball was nonpulsatile and nonreducible.

Skull films were normal. Computed tomography (CT) scan showed a nonenhancing oval cystic lesion with a hyperdense rim within the muscle cone. The optic nerve was not identified. On CT, there was mass effect on the medial orbital wall and a septum running through the cyst (Fig. 1).

In April 1987, he was operated on at Pediatric Surgical Service for cysts in his right lung. Two weeks later, surgical intervention was performed.
through a transcranial approach in our clinic. An echinococcus cyst containing approximately 8 ml of hydatid fluid, located within the muscular cone, was removed. Unfortunately, it was ruptured due to poor location during the surgical intervention. Therefore, the surgical area was generously washed with hypertonic saline solution. Pathological examination of the specimen was consistent with a diagnosis of Echinococcus granulosus infestation.

The patient was readmitted 7 months later because of recurrent left-sided exophthalmos. Neuro-ophthalmological findings suggested an expanding lesion of the orbit. A repeat CT scan again showed growth of a cystic lesion with a thicker cavity wall in the left orbit located partially intracranal (Fig. 2). In view of the location of the lesion, the patient was treated with mebendazole, an antihelminthic drug, for 10 months and remained well at follow-up. A CT scan in August 1988 showed a considerable reduction in size of the lesion (Fig. 3), and when repeated again in December 1990, three years after the start of treatment, it showed almost complete resolution and resultant small calcified lesion (Fig. 4).

*The generic name of mebendazole is [metil(S-benzoil benzimidazol-2-il)karbamat].

**FIG. 1.** A well-circumscribed, low-density intracranal cyst with hyperdense rim on precontrast (A) and postcontrast (B) axial CT scans. Note the septum (small arrows) running through the cyst and slight bowing of the wall (large arrows).

**FIG. 2.** Precontrast (A) and postcontrast (B) scans showing the recurrence of hydatid cyst which ruptured during first operation, with a thicker cavity wall. Again noted is the enlargement of the left orbit with bowing of the medial wall (arrows). In addition, the left optic nerve appears slightly swollen.
FIG. 3. Follow-up CT scan, 9 months after the start of antihelminthic drug, demonstrates marked decrease in the size of the cyst.

DISCUSSION

Hydatid disease, a parasitic infectious disease caused by the larval stage of *Echinococcus granulosus*, is endemic in Turkey, (3) and it usually involves all three hosts of the epidemiological chain consisting of sheep, dog, and humans (16). Humans are intermediate hosts; the parasite enters the host in childhood, because of the child's close contact with dogs, and it becomes symptomatic in following years. Although the hydatid cyst affects almost every organ in the body, it generally occurs in the liver and lungs. Orbital localization is rare (1).

Clinical symptomatology, in general, is not diagnostic (7) and immunodiagnosis of the hydatid cyst is always negative as well (6). At the present time, however, CT has advanced significantly the diagnosis and management of orbital lesions (7). The first case of an orbital hydatid cyst studied by CT was reported by Özgen et al. (4). In the following years, orbital hydatid cysts have been reported with increasing frequency with the help of the CT scanner, especially from the Middle East (7,8), the Mediterranean Basin (1,6,9), and India (10). Its CT characteristics differentiate it from other intraorbital space-occupying lesions. The CT appearance of a hydatid cyst has been described as a hypodense, nonenhancing, oval homogenous mass with a hyperdense rim (1-3,4,6-10). Our case, in addition, showed bowing of the medial orbital wall without bony erosion and evidence of a septum running through the cyst. Other cystic lesions of the orbit occurring in childhood such as dermoid cyst, encephalocele, sinus mucocele, and teratoma do not display septations and bone displacement. Thus it is important to know the presence of these features in the differential diagnosis of unilateral exophthalmos in patients from countries where echinococcosis is endemic.

The only current definitive treatment is total surgical excision of the cysts when possible (1-13). At the surgery, aspiration or opening of the cyst should be avoided unless removal cannot otherwise be accomplished (11). When the cyst wall was torn, the beneficial effect of irrigation with hypertonic saline solution as an adjunct to the surgical treatment is reported (4,13). In our case, the area of spillage was irrigated with this solution, but the recurrence of the disease developed in the same area. Pearl et al. reported that mebendazole was
exceedingly active against *Echinococcus granulosus* cyst (12). In the present case, treatment with an antihelminthic drug was started and caused complete clinical and radiological response with a small calcified residue. As occurs with cerebral cysticercosis and tuberculosis (14,15), echinococcosis may eventually calcify and regress into scars after medical treatment (4,16). To our knowledge, the present case is the first report of a calcified residue seen in a patient with orbital hydatid cyst following treatment.

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REFERENCES

Reflex Blink to Visual Threat

Grant T. Liu, M.D. and Michael Ronthal, M.B.Bch.

The requisite visual modalities for the reflex blink to visual threat have not been thoroughly studied. We identified five patients with different focal cerebral lesions documented on computerized tomography scan who had abnormal blink-to-threat reflexes. One had a homonymous hemianopia secondary to posterior cerebral artery occlusion; another had a unilateral parietal neglect; and a third had a frontal neglect. They did not blink in response to visual stimuli contralateral to their lesion. A cortically blind patient and one with Balint's syndrome did not have a blink response. Observation of these and other similar patients and animals previously reported suggests that the blink-to-threat reflex is cortically mediated and requires intact primary visual cortex as well as higher order mechanisms for visual attention mediated in the inferior parietal lobule and frontal eye fields.

**Key Words:** Blink—Reflex—Threat—Neglect—Attention—Balint's syndrome.

When an object is brought suddenly toward the open eyes of a normal individual there is a prompt blink response. Obviously the optic nerve serves as the afferent pathway ... (and) the cortex almost certainly must be in the reflex arc, but what part it plays is not clearly understood.

F. B. Walsh
"Reflex Blinking and the Menace Response" (1)

The blink reflex to threat or menace is a standard bedside method for testing visual field defects (2–4), especially in patients uncooperative with standard visual confrontation (5). In response to a sudden, unexpected gesture directed toward the eyes, a normal person promptly contracts both orbicularis oculi to close the eyelids momentarily. Despite its common use, the pathways and the requisite cortical modalities for this response still remain uncertain. In spite of Walsh's statement (1), studies of the role of the cortex in the blink reflex are sparse (6). In 1929 Eihlers (7) wrote, "The blinking reflex for threatening danger requires involvement of that portion of the cerebral cortex which is the seat of visual perception," implying the need for an occipital cortex. Moses (8) felt the reflex was cortically mediated and required an intact occipital lobe and "its connections with the Rolandic area." Ross Russell (9) invoked an occipitopontine pathway without involvement of the frontal lobe. Hoyt and Loeffler (10) and then Miller (4) added that parieto-occipital and parietotemporal areas may be necessary for the blink-to-threat reflex. Itoh et al. (11), on the other hand, suggested that the reflex could be mediated entirely in the brain stem.

We identified five patients with varied focal cortical lesions and absent blink-to-threat reflex. Although others have made similar anecdotal observations, to our knowledge no comprehensive review on the reflex blink to visual threat exists. Based on our patients and other similar cases and animal studies reported in the literature, we propose that the lack of a blink-to-threat reflex does...
not always reflect a visual field deficit, but instead could also indicate a defect in visual attention.

**METHODS**

Patients with cortical lesions documented on imaging studies who had absent blink to visual threat were identified from the inpatient services of the Beth Israel and Brigham and Women's Hospitals from February 1990 to May 1990. All patients were examined by at least one of us (GTL).

The examiner elicited the blink-to-threat reflex by suddenly thrusting his fingertips towards the patient's eyes from the periphery. Menacing from the periphery was preferred because it was difficult to decide which nasal hemifield detected stimuli that was directly in front of the patient. Covering one of the patient's eyes to test monocular fields was felt to detract from the surprise of the threat. Likewise, auditory cues were not given to direct the patients attention. Jerking the entire hand with the palm or the back of the hand facing the patient was avoided in order to prevent evoking a tactile blink reflex by moving air onto the cornea (12). The blink reflex was considered intact if there was either partial or complete closure of the eyelids. Visual fields were determined by confrontation (5), but in some cases formal Goldmann perimetry was also obtained.

Patients with significant ophthalmological disease affecting the cornea, lens, vitreous, choroid, retina, optic nerve, and chiasm, as well as patients with nuclear and peripheral facial nerve lesions, diseases of the neuromuscular junction, and myopathies involving the orbicularis oculi were excluded. Comatose patients were also excluded.

Five representative patients with focal cerebral lesions and abnormal blink-to-threat reflexes were identified. All patients blinked spontaneously, indicating completeness of the facial nerve motor unit. The ages of the patients ranged from 36 to 81; four were men. Three had acute cerebral infarctions; one had intracerebral hemorrhages; and another had intracerebral cyst formation.

**CASE REPORTS**

**Patient 1**

A 67-year-old man with hypertension and diabetes was admitted with complaints of unsteadiness and difficulty seeing with his left eye. His mental status was normal, but he drew a clock with numbers only on the right side. His corrected visual acuity was 20/20 OU. Funduscopic examination was normal. Goldmann perimetry demonstrated a dense congruous left homonymous hemianopia with macular sparing, and he did not blink in response to threatening gestures presented in the left hemifield, but he did blink in response to those in the right. His eye movements and optokinetic response were normal. The rest of his neurological examination was significant for mild left facial weakness, a mild left pronator drift, and an increased left biceps reflex. Computerized tomography (CT) scan of the brain revealed decreased attenuation in the right occipital lobe, consistent with infarction (Fig. 1). The mild left hemiparesis and congruous homonymous hemianopia with macular sparing suggested posterior cerebral artery occlusion (13-15).

**Comment.** This patient, who developed an occipital lobe infarct, did not blink to threat in his blind hemifield.

**Patient 2**

A 75-year-old man presented with bilateral cystic occipital lobe lesions secondary to resection of a parasagittal occipital meningioma 3 years previously. The cysts were removed initially in 1988, but they recurred. In late 1988, he developed right-sided weakness that was felt to be associated with a lacunar infarction. He required a ventriculoperitoneal shunt for treatment of hydrocephalus in January 1990; he was then readmitted in April.
for further surgical drainage of the occipital
cysts.

On neurological exam he was abulic, but he fol­
lowed simple commands. Funduscopic examina­tion
was normal, and his pupils were briskly reactive
to light. The patient appeared not to see any­
thing. He did not blink to visual threat in any field.
He was unable to point or direct his gaze to any
face or object requested. His eyes roved randomly.
On command, he could move his eyes conjugately
left and right, but he had some difficulty with up­
gaze. Optokinetic responses were absent. The rest
of his exam was notable for a mild right hemipa­
resis and a right extensor plantar response.

Computed tomographic scan of the head re­
vealed the occipital cysts, a left frontal subdural
fluid collection, and a shunt lying in the frontal
horn of the right lateral ventricle (Fig. 2).

Comment. In this patient bilateral occipital lobe
lesions produced cortical blindness (16). The pre­served pupillary reflexes, mediated in the pretec­
tum (17), indicate intact pregeniculatc visual path­
ways. He did not have optokinetic nystagmus,
consistent with the diagnosis (16), and he had no
blink to threat.

Patient 3

A 36-year-old man with a postviral dilated car­
diomyopathy underwent a cardiac transplantation
on May 2, 1990. After surgery he developed ven­
tricular tachycardia, necessitating cardioversion;
right ventricular failure, requiring an intra-aortic
balloon pump and a right ventricular assist device;
and disseminated intravascular coagulation. His
platelet count fell to 45,000. After an episode of
hypotension on May 4, 1990, he became unresponsive
to voice or deep pinch, and he made no sponta­
nous limb movements. Head CT demonstrated
bilateral parieto-occipital hemorrhages with signifi­
cant surrounding edema and mass effect.

By May 11, 1990, he was alert, attentive, and
able to follow simple verbal commands. He did not
blink to threat. His pupils were 4 mm bilaterally
and reactive. When asked to do so, he was able to
direct his gaze in all directions.

One week later he was able to recognize bright
light and detect movement, but in the left homon­
ymous hemifield only. He was not able to follow
visual targets. He was unable to count fingers, but
when verbally instructed he held up the correct
number of fingers. He wore his eyeglasses and
claimed to watch television, although he was un­
able to describe what he saw.

Dilated funduscopic examination at this time re­
vealed normal discs, vessels, maculae, and periph­
ery. Repeat head CT documented the bilateral pa­
rieto-occipital hemorrhages (Fig. 3A).

Five weeks postoperatively his vision had recov­
ered significantly, although there were still notice­
able deficits. Goldmann perimetry revealed an in­
ferior homonymous altitudinal hemianopia with
sparing of the temporal crescent (18) OS (Fig. 3B
and C). There was still no blink to threat in any
visual field. He was able to look left and right on
command. On attempting to shift gaze to an object
in the periphery, he had difficulty locating it with­
out ‘scanning’ for several seconds. When he at­
tempts to reach for objects, he frequently missed
his target, especially with his right arm. Finally, he
was given a postcard of a lake and asked to iden­
tify the scene. His eyes searched over the card for
several seconds. Correctly, he said “I see chairs .
. . I see flowers . . . I see pines,” and then, after
15 seconds of thought, he guessed, “Is this a lake
scene?”

Comment. Bilateral parieto-occipital hemorrhages
in this patient initially resulted in cortical blind­
ness. He first manifested Anton’s syndrome (16);
when he improved, he displayed the elements of
Balint’s syndrome (19) (see below). He had no
blink to threat.

Patient 4

An 80-year-old right-handed woman with a his­
tory of hypertension and a stable thoracic aortic
aneurysm was admitted after falling at home.
She was mildly inattentive, but her language was normal. She was initially totally unaware of the left hemispace and denied that her left arm belonged to her. She preferred to look to her right, but she had normal extraocular movements. Her left face, arm, and leg were paretic, and the left plantar response was extensor.

The next day she was felt not to have a visual field deficit because, with verbal cues, she acknowledged objects and individuals to her left. With double simultaneous stimulation she extinguished visual and tactile stimuli on the left. She did not blink to threat from the left periphery but did from the right.

Head CT demonstrated an infarct involving the right parietal lobe but also extending into the pos-
terior portion of the frontal lobe (Fig. 4). Magnetic resonance imaging of the chest revealed dilatation of the entire thoracic aorta with dissection extending from the descending aorta into the abdomen. Thrombus occluded a false lumen. She was thought to have had an embolus from aortic dissection, and she received anticoagulant treatment.

Comment. This woman, who had a right parietal infarction, neglected visual stimuli in the left hemispace and did not blink to threat from the left. However, when her attention was directed to the left with auditory cues, it was clear she had no major visual field deficit.

Patient 5

A 68-year-old right-handed hypertensive man developed right-sided weakness after coronary artery bypass grafting. He was thought to have had a subendocardial myocardial infarction with hypotension during the surgery.

The first day after surgery he did not move his right side as well as his left. He was drowsy but easily arousable. There was a tendency to ignore the right side, but he had no visual field deficit. He easily recognized objects on his right if his attention was directed that way. He did not blink in response to threatening gestures from the right periphery, but he did from the left. Funduscopic examination was normal. Conjugate extraocular
movements were present, but gaze to his right was incomplete. His face and arm were paretic on the right, and his right brachioradialis and biceps reflexes were increased. The right plantar response was extensor.

Language examination was limited because he was initially ventilator-dependent. On the fifth postoperative day he was extubated, and his speech was nonfluent and dysarthric. He followed simple verbal commands, but he had difficulty with reading aloud, naming, and repetition.

Heat CT demonstrated two hypodense areas in the left frontal lobe: one in the lateral aspect, which also involved the head of the caudate, putamen, and anterior limb of the internal capsule; and the other in the medial and superior portion (Fig. 5). These were felt to be acute infarcts in the distributions of the left middle cerebral and anterior cerebral arteries, respectively. Carotid noninvasive studies revealed a totally occluded left internal carotid artery.

**DISCUSSION**

An absent blink-to-threat reflex could result from a lesion in the afferent visual pathway by interrupting the presentation of a full array of visual information from eye to brainstem and cortex. Alternatively, a defect in the efferent pathway to orbicularis oculi might abolish the ability to blink. We excluded patients with these mechanisms and will confine our discussion to “central” mechanisms.

Teleologically, reflex blinks are mechanisms for eye protection in response to external stimuli (21). Blink to threat should be distinguished from other reflex blinks that are mostly brainstem mediated, such as the orbicularis oculi reflex (4,8,22,23), the corneal blink reflex, and the cochleopalpebral reflex (4). The reflex blink to light or dazzle requires an intact optic nerve and connections to pretectum, but not cortex (4,24,25).

Neonates blink in response to light and corneal stimulation, and the light reflex occurs as early as 25 weeks of gestation (26,27). Newborns also have the ability to fix, follow, and be alert to visual stimuli, and most have optokinetic responses (26,28). However, reflex blink to visual threat is not present in neonates (21), and it does not emerge until the infant is 2–4 months of age (12,26). The reflex is believed to be a learned response (26). This suggests that the blink to threat is not a primitive reflex, but one that requires higher-order cortical processing of a stimulus more complex than a flash of light or touch on the cornea.

Further evidence for the role of the cortex in blink-to-threat reflex is its absence in patients who are effectively decorticate. Keane (24) reported a 54-year-old woman who suffered from anoxic neocortical death with isoelectric encephalograms and absent visual evoked responses. Her corneal and cochleopalpebral reflexes were intact, and her blink-to-light reflex persisted, although she did not blink to visual threat. Pathological examination revealed almost complete cortical neuronal loss but preservation of the brain stem (24). Tavy et al. (25) described a patient with similar clinical findings who at postmortem was found to have diffuse hypoxic changes of the cerebral and cerebellar cortices because of a cardiac arrest. Hill et al. (29) described a 1-month-old hydranencephalic girl who “did not respond to thrust movements” but blinked to light. Postmortem examination revealed an intact brain stem, cerebellum, and basal ganglia, and a thin membrane—most likely residual cerebral cortex—surrounding a fluid-filled cavity.

Our patients with focal cortical lesions and ab-

![FIG. 5. In patient 5, these infarctions in the medial (anterior cerebral artery territory) and lateral (middle cerebral artery territory) portions of the left frontal lobe led to right-sided neglect.](image-url)
sent blink-to-threat reflex offered an opportunity to examine the modulation of the response by the cortex. We shall discuss the lesions topographically.

Occipital Lobe

Patients 1, 2, and 3 developed blink-to-threat reflex abnormalities as a result of occipital lobe lesions. Patient 1 did not blink to threat in his blind hemifield, and cortically blind patients 2 and 3 had no blink to threat.

Several reported cases of cortical blindness have also demonstrated absent blink-to-threat reflex. Cases 3 and 4 of Barnet et al. (30) had normally reactive pupils and blinked to light but not "to menace." Silverman et al. (31) and Denny-Brown (32) described similar patients. Multiple references (16,33,34) list loss of blink-to-threat reflex as one of the principle clinical features of cortical blindness.

Experimental studies in monkeys (32,35) confirm the above observations. Marquis and Hilgard (35) found that a monkey with one occipital lobe removed did not blink to threat in the contralateral hemifield. After removing both occipital lobes, the researchers demonstrated that the pupillary response was unaffected, but that blinking in response to "threatening gestures" was absent in all visual fields (35). Denny-Brown (32) ablated area 17 bilaterally and produced similar findings. These observations and our own suggest that the blink-to-threat response requires an intact contralateral occipital lobe and primary visual cortex.

Patient 3's initial ability to detect light and motion in his left homonymous hemifield (36,37) without a blink-to-threat reflex implies that the response requires more than those visual modalities. Denny-Brown's cortically blind patient (32) similarly improved to appreciate moving objects and light and also did not blink to visual threat. Similar patients with "blindsight" after unilateral or bilateral occipital lesions lose object recognition, but in some instances they may have an ability to locate light sources and detect moving targets in affected fields via retino-tectal-pulvinar pathways (38-43). It would be informative for one of these patients to be tested for blink to threat.

Parietal Lobe

The findings in patient 4 demonstrate that an individual with unilateral visual inattention from a right parietal lesion (44-47) may have an absent blink to threat in the neglected left hemispace, despite (presumably) intact visual fields.

This observation suggests that attentional mechanisms are important for blink to threat. The posterior parietal lobe, frontal lobe, and cingulate gyrus are instrumental in proposed cortical networks for directed attention (47-51). Dorsolateral area PG, located in the inferior parietal lobule or area 7, is the pivotal parietal lobe structure (52,53). It receives visual information relayed by polymodal sensory cortex from striate, peristriate, and inferotemporal cortices (49). An intact area PG is probably necessary for an intact blink-to-threat reflex. In 1881 Munk (54) observed that monkeys with posterior parietal-anterior occipital cortex lesions did not blink in response to contralateral threat. Similarly, Heilman et al. (55) noticed that monkeys with inattention to the contralateral space from ablation of the inferior parietal lobule had a diminished blink-to-threat response in the unattended contralateral hemifield, despite intact visual fields. Shibutani et al. (6), recording from monkey PG neurons and electromyography of the orbicularis oculi muscles, demonstrated a population of PG neurons which caused blinking when stimulated directly. Furthermore, when they moved a 10 x 20-cm plate quickly towards the monkey's face, the same neurons fired rapidly, and then, after a delay of 190 msec, the monkey blinked.

The results suggest that certain PG neurons are responsive to visual threat and have the capability of coupling the striate cortex's perception of the threat with motor pathways for blinking. This is consistent with PG's proposed role in one of the models for attention (49): linking the visual stimulus of motivational significance (threat of injury to the eye) with motor behavior (eyelid closure). Thus the absence of a blink-to-threat response in the setting of injury to the inferior parietal lobule may be indicative of a defect in visual attention.

In humans, the counterpart to monkey area 7 would correspond either to superior parietal lobule (human area 7) or inferior parietal lobule (human areas 39 and 40) or both (45). The parietal infarct in patient 4 involves at least areas 39 and 40 on the right (56), causing the contralateral neglect and a loss of blink-to-threat response from the left as well. Though motor cortex was likely involved, the frontal eye fields, area 8, were spared (see below).

Balint's Syndrome

Balint (57) first analyzed this symptom complex which was later elaborated by Holmes (58), of oculomotor apraxia (a deficit in shifting gaze), optic ataxia (a defect in reaching under visual guidance), and simultanagnosia (59). The lesions that cause

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Balint's syndrome are typically bilateral and occipitoparietal in areas 7, 19, and sometimes 39 (60), zones highlighted above as important for visual attention and foveal fixation. As in patient 3, the visual field defect is usually inferior (61,62), but sometimes the fields are normal (59).

Like our patient, five of the six patients Holmes reported in 1918 did not ‘blink or otherwise respond to any threatening action, as when a hand or other large object was suddenly swung towards their faces’ (58). He believed that ‘blinking seems to be a forebrain reflex dependent on the functioning of centres which were injured by the lesions presented in these cases’ (58). Holmes' second patient blinked when his own arm was moved passively towards his face, and Holmes therefore surmised that the absence of the blink reflex resulted from defective distance perception.

Several other patients with Balint’s syndrome and absent blink-to-threat reflexes have been reported (61–65), and two of the more recent authors (63,64) implied that the lack of a blink reflected a defect in visual attention. Hausser et al. (63) included the absence of the blink reflex under “disturbance of visual attention.” Pierrot-Deseilligny et al. (64), whose patient sustained bilateral damage to the inferior parietal lobules, used the loss of a menace response to demonstrate a “neglect of some peripheral stimuli.” The loss of a blink-to-threat reflex may simply be a manifestation of the “extreme narrowing of attention” (66,67), an inability to notice any object outside foveal vision, seen in Balint’s syndrome.

As suggested in the previous section, unilateral damage to the inferior parietal lobule causes a contralateral defect in attention to visual stimuli and loss of blink-to-threat reflex. By extension, bilateral injury in Balint's syndrome results in a deficit in visual attention for the whole periphery as well as complete absence of a blink-to-threat response.

Frontal Lobe

Patient 5 had a defect of directed attention to the right hemispace and did not blink to visual stimuli on the right. Frontal lobe neglect is well recognized in humans (68,69), can be very dense (45), and usually results from a right-sided lesion. Cogan (70) used the term “pseudohemianopsia” to refer to patients with this disorder.

Kennard's experiments (71,72) in monkeys relate unilateral lesions specifically in area 8, the frontal eye fields, to pseudohemianopsia and blink-to-threat reflex abnormalities. In addition to developing ipsilateral conjugate eye deviation without limb weakness, the animals ignored food on the side contralateral to the lesion but noticed the food as soon as it was brought past midline to the ipsilateral side. Blink to visual threat was absent on the contralateral side. These findings were independent of eye position, and lesions to other frontal lobe structures such as primary motor cortex (areas 4 and 6) and frontal association fields (areas 9, 10, and 11) did not result in these visual disturbances. After bilateral ablation of area 8, the animals had no blink to threat from either side, and they bumped into large objects as if they had no vision. Nonetheless, they retained an ability to reach and grasp for objects; therefore Kennard believed the monkeys were not totally blind. Instead, she concluded that lesions to the frontal eye fields caused either a deficit in responding to visual stimuli or an inability to recognize them (71,72). Subsequent investigators (73–75) have repeated these experiments with similar findings.

One of the models for directed attention (49) predicts that unilateral frontal lobe lesions result in contralateral neglect by disrupting the motor programs for responding to new stimuli. An absent blink-to-threat reflex in the setting of frontal lobe injury therefore might be the result of a defect in the motor plan for eyelid closure. On the other hand, the parceling of motor components to frontal cortex and of sensory components to parietal cortex is not necessarily exclusive (49,51,76). Most likely, the frontal lobe also contains minor mechanisms for sensory integration as well as a motivational map. Thus, the loss of a blink-to-threat response in patients with frontal neglect may also be explained by a defect in visual spatial recognition.

The blink-to-threat reflex does not require intact motor cortex. Lessell (77) reported a patient with presumed amyotrophic lateral sclerosis and evidence of bilateral pyramidal tract involvement, who could not close his eyelids voluntarily but blinked to visual threat. Ross Russell (9) described three individuals with Creutzfeldt-Jakob disease with pyramidal tract degeneration documented on postmortem, who similarly could not blink on command but blinked to threat. In both reports, the patients also continued to blink spontaneously and in response to corneal stimulation and loud noise. Lessell (77) and Ross Russell (9) argued that the deficiency in voluntary eyelid closure resulted from bilateral damage to cortical motor neurons and not from a facial dyspraxia.

Kennard’s results (71,72) instead suggest that the blink-to-threat response depends upon an intact contralateral frontal eye field. Electrical stimulation of the posterior bank of the frontal eye field
in monkeys produces blinking (78, 79), although this eyelid closure may not be the same as that elicited in a blink to threat. Area 8 may mediate the motor plan for the blink in response to threat or contain the actual corticobulbar neurons.

As discussed previously, neurons in area PG (6) can also cause blinking. It is likely that PG elicits blinking by way of the frontal eye fields (80), but the reverse may be true, because PG makes descending connections directly to the brain stem (81). On the other hand, PG or the frontal eye fields may require communication first with the various subcortical structures such as cingulate gyrus and putamen that can elicit eyelid closure (4). The pathway governing the blink-to-threat reflex from these cortical areas mediating attention to the facial nerve nuclei in the pons is not certain.

CONCLUSION

The blink-to-visual-threat reflex thus requires intact striate cortex as well as higher-order visual attentional mechanisms mediated in the inferior parietal lobules and frontal eye fields. Therefore, an absent blink to threat by itself is nonlocalizing.

Acknowledgment: The authors wish to thank Drs. M.-Marcel Mesulam and Martin A. Samuels for their helpful hints and discussion.

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The Miller Fisher Syndrome
Review of the Literature

Peter Berlit, M.D. and Josef Rakicky, M.D.

The triad of ataxia, areflexia and ophthalmoplegia was first described as a variant of the Guillain-Barre syndrome in 1932 by Collier. In 1956, Miller Fisher reported three patients with ataxia, areflexia, and ophthalmoplegia as a separate entity. Since then, 223 cases of Miller Fisher syndrome have been published. The male/female ratio is 2:1 with a mean age of 43.6 years at the onset of the disease. A viral infection preceded the neurological symptoms in 71.8% of cases with an average symptom-free interval of 10 days. First symptoms were diplopia (38.6%) or ataxia (20.6%). An areflexia was present in 81.6% of cases. Cranial nerves other than the oculomotor nerves were involved in 127 cases (56.9%): cranial nerves 7 (45.7%), 9 and 10 (39.9%), and 12 (13%) were involved. In 53 cases a tetraparesis occurred. An elevated protein value was present in 134 patients (64.4%); cerebrospinal fluid findings were normal in 56 patients. Eighteen patients showed a mild pleocytosis. Besides the cerebellar type of ataxia, initial disturbances of consciousness (n = 8), supranuclear oculomotor signs (n = 22), and pathology findings in electroencephalography (n = 38), computed tomography (n = 8), and magnetic resonance imaging (n = 2) were reported as evidence for a central nervous system involvement in the Miller Fisher syndrome. The prognosis of Miller Fisher syndrome was good—recovery occurred after a mean time period of 10.1 weeks. Residual symptoms were present in 74 cases (33.2%), and a recidivism of the Miller Fisher syndrome was reported in seven patients. Eight patients died. Of six patients with autopsy findings, four exhibited central nervous system lesions. The Miller Fisher syndrome is apparently a variant of the Guillain-Barre syndrome with frequent central nervous system involvement and a benign outcome in the majority of cases.

Key Words: Miller Fisher syndrome—Guillain-Barre syndrome—Areflexia—Ataxia—Ophthalmoplegia.

As early as 1 year after the first description of the Guillain-Barre syndrome in 1916 (1), variants with involvement of the cranial nerves and the central nervous system were reported (2-4). The triad of ataxia, areflexia, and ophthalmoplegia was first described as a variant of the Guillain-Barre syndrome in 1932 by Collier (5). During the following years, there were several reports about the combination of bilateral ophthalmoplegia and widespread paralysis of the extremities in acute polyneuritis (6-11). In 1956, Miller Fisher reported three patients with ataxia, areflexia, and ophthalmoplegia without prominent signs of peripheral neuropathy as a separate entity (12). Since then, patients presenting with ataxia, areflexia, and ophthalmoplegia as their leading symptoms are referred to as having the Miller Fisher syndrome. (Since one author is responsible for defining this condition, the hyphen between the names should be avoided.)

Since 1956, 223 cases of Miller Fisher syndrome have been described in the world literature. The majority of cases are cited under the name of Miller Fisher, some primarily as ataxia, areflexia, and ophthalmoplegia with reference to the Miller Fisher syndrome. In the discussion about the localization of ataxia, areflexia, and ophthalmoplegia, both a pure peripheral nerve affection (13-16) and a primary central nervous system lesion in the sense of a brainstem-encephalitis (17-21) are suggested. In this report, we try to reevaluate the clinical picture, the course, and the possible pathogenesis and localization of Miller Fisher syndrome by a review of the literature.

AGE AND SEX DISTRIBUTION

The male/female ratio of the 223 patients in the literature is approximately 2:1. The mean age at the onset of the disease is 43.6 years. There are reports of about 32 (14.3%) children with Miller Fisher syn-
There were 21 boys (9.4%) and 11 girls (4.9%). In the reports of adult patients, there were 113 men (50.7%) and 51 women (22.9%). In 27 cases, no sex was given (12.2%). The age of the oldest patient was 80 years; the youngest child was 14 months old. The sex distribution in the different age groups of all the patients reported is summarized in Fig. 1.

As in the Guillain-Barre syndrome, the majority of patients with Miller Fisher syndrome develop their symptoms after some kind of viral infection (12-80); the respiratory tract (n = 132; 59.2%) is by far the most common site of infection. The various events that precede ataxia, areflexia, and ophthalmoplegia are shown in Table 1. The average time between the preceding event and the Miller Fisher syndrome was 10 days, the longest interval being 5 weeks. In 24 cases (12.6%), no preceding illness was mentioned. Only 12 of the reported patients (5.4%) had an elevated leukocyte count at the time of admission.

INITIAL SYMPTOMS

The initial symptoms of Miller Fisher syndrome are given in Table 2. Diplopia and ataxia were responsible for one-third and one-fourth of initial symptoms, respectively. In most patients, the full picture of ataxia, areflexia, and ophthalmoplegia was reached in 5 to 10 days, so, in general, a subacute course of the disease can be presumed.

Cardinal Symptoms

A complete ophthalmoplegia including the parasympathetic fibers to the m. sphincter pupillae was described in 109 patients (48.9%). A pure external ophthalmoplegia was reported in 72 patients (32.3%). In 42 patients (18.8%), sufficient data were missing. An accompanying unilateral or bilateral ptosis was present in 105 patients (47.1%). The ophthalmoplegia developed asymmetrically in 108 patients. Supranuclear ocular symptoms in Miller Fisher syndrome were described by several investigators. Signs of internuclear ophthalmoplegia (50, 59, 63, 72, 75, 76, 81), the one-and-a-half-syndrome (19), the Parinaud syndrome (82), and preserved optokinetic nystagmus in complete ophthalmoplegia (34, 41, 46, 54, 56, 59, 67, 71, 72) were mentioned. Meienberg described one patient with convergence spasms (48).

The ataxia was characterized as cerebellar in the majority of cases, with stand and gait ataxia suggesting a lesion of the paleocerebellum. In 201 patients, ataxia was attributed to be cerebellar in origin (90.1%). Only two patients presented with a sensory ataxia (0.9%) (35, 83). In 20 cases (9%), data were missing. Areflexia was documented in 182 patients (81.6%): in 41 cases no description of the reflex status had been given (18.4%).

Other Symptoms

Involvement of cranial nerves other than the ocular nerves was cited in 127 patients (56.9%). The facial nerve was most frequently affected (n = 102; 45.7%), followed by the lower cranial nerves: dysphagia as a possible sign of cranial nerves 9 and 10 lesions (n = 89; 39.9%) and dysarthria as a possible symptom of cranial nerve 12 paresis (n = 29; 13%). Only in 2 patients was dysarthria described as cerebellar (56).

Other involved cranial nerves were 1 (n = 2), 5 (n = 11), 8 (n = 2), and 11 (n = 6). In facial palsy,
a preserved Bell phenomenon instead of complete ophthalmoplegia was observed by some investigators (12,21,23,26,34,35,67,84). Only in 2 patients was facial palsy of central origin described (50,73). A paresis of the extremities was described in 63 patients (28.3%). In only 1 case published as Miller Fisher syndrome was there a severe tetraparesis (56). Most of these patients presented with a mild accompanying tetraparesis (n = 54). A hemiparesis was present in 6 patients (73,79,85). In one of his original patients, Miller Fisher described a monoparesis of the right arm (12).

Sensory symptoms were present in 99 patients (44.4%). In the majority (n = 52), there were paresthesias and dysesthesia of all four extremities. Both legs of 39 patients were affected. Involvement of the arm and leg on one side of the body or of one arm only were each described in 4 circumstances. A palhypesthesia was observed in 42 patients (18.8%), but it was never severe enough to explain the ataxia of the patients.

Other reported symptoms include headache (n = 34), disturbance of consciousness (n = 24), fever (n = 13), vomitus (n = 8), and irritability (n = 3). In 9 patients, plantar responses were reported as being extensor (17,18,33,62,70); 5 patients developed bladder problems during the course of their disease (20, case 8; 40, 69, 79, cases 2 and 4). Epileptic fits were reported by Bickerstaff (20) and Al Din (17). Myoclonias, tremor, and other extrapyramidal symptoms were reported by Bickerstaff (20) and Ropper (86). A respiratory insufficiency developed during the course of the disease in 11 patients.

**CEREBROSPINAL FLUID FINDINGS**

In most of the reports, cerebrospinal fluid findings are mentioned (n = 208; 93.3%) but usually without a statement about the time of lumbar puncture. An elevated protein value was present in 134 patients (64.4%), 2.8 g/l (87 patients) and 5.2 g/l (67 patients) being the highest protein measurements. The rise in protein usually developed over 1-3 weeks. Eighteen patients showed an initial pleocytosis (8.1%). The highest cell count was 1,350/3 cells (17). Cerebrospinal fluid findings were normal in 56 cases (26.9%).

**NEUROPHYSIOLOGICAL FINDINGS**

Only a few investigators report on quantitative electrophysiological findings; some methods were mentioned only in single cases, which makes the findings difficult to interpret. Generalized slowing of electroencephalography activity was documented in 36 of 66 available case reports (54.5%). Localized slowing was mentioned in only 2 circumstances (12,17). There was no case with epileptiform discharges. Electromyography findings were given for 99 patients. Signs of demyelination were present in 38 of these patients (38.4%): in 11 patients a primarily axonal lesion was suggested (11.1%). Combined findings were obtained in 18 patients (18.2%). In 32 patients, the electromyography findings were normal (32.3%). Pathological acoustic evoked potentials findings have been reported twice (17,88); the blink reflex was pathological in one case report (61).

**NEURORADIOLOGICAL FINDINGS**

Computed tomography examinations were performed for 66 patients. Pathological findings were infratentorial hypodensities in eight patients (12.1%) (17,46,75). The majority (n = 58; 87.9%) of

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**TABLE 1. Antecedent events in Miller Fisher syndrome (n = 223)**

<table>
<thead>
<tr>
<th>Antecedent event</th>
<th>n (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory infection</td>
<td>132 (59.2)</td>
<td>12, 14, 15, 17, 18, 21, 24–37, 39, 41, 44–53, 55–59, 62–70</td>
</tr>
<tr>
<td>Gastrointestinal infection</td>
<td>19 (8.5)</td>
<td>20, 25, 32, 36, 38, 40, 42, 55, 60</td>
</tr>
<tr>
<td>Childhood infection</td>
<td>4 (1.8)</td>
<td>17, 20, 50, 54</td>
</tr>
<tr>
<td>Tonsilitis</td>
<td>1 (0.4)</td>
<td>15</td>
</tr>
<tr>
<td>Urogenital infection</td>
<td>1 (0.4)</td>
<td>19</td>
</tr>
<tr>
<td>Spondylitis</td>
<td>1 (0.4)</td>
<td>61</td>
</tr>
<tr>
<td>O fever</td>
<td>1 (0.4)</td>
<td>81</td>
</tr>
<tr>
<td>Others</td>
<td>10 (4.5)</td>
<td>43, 47, 56</td>
</tr>
<tr>
<td>Vaccination</td>
<td>3 (1.3)</td>
<td>46, 57</td>
</tr>
<tr>
<td>Delivery</td>
<td>2 (0.9)</td>
<td>26, 52</td>
</tr>
<tr>
<td>Alcohol excess</td>
<td>2 (0.9)</td>
<td>33, 71</td>
</tr>
<tr>
<td>Cholesteatom surgery</td>
<td>1 (0.4)</td>
<td>17</td>
</tr>
<tr>
<td>Digitalis intoxication</td>
<td>1 (0.4)</td>
<td>16</td>
</tr>
<tr>
<td>Insect bite</td>
<td>1 (0.4)</td>
<td>22</td>
</tr>
<tr>
<td>None</td>
<td>24 (10.8)</td>
<td></td>
</tr>
<tr>
<td>No data available</td>
<td>39 (17.4)</td>
<td></td>
</tr>
</tbody>
</table>

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**TABLE 2. Initial symptoms of Miller Fisher syndrome (n = 223)**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No. cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diplopia</td>
<td>86 (38.6)</td>
</tr>
<tr>
<td>Ataxia</td>
<td>66 (29.7)</td>
</tr>
<tr>
<td>Headache</td>
<td>7 (3.1)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>7 (3.1)</td>
</tr>
<tr>
<td>Facial palsy</td>
<td>5 (2.2)</td>
</tr>
<tr>
<td>Paresthesias of arms or legs</td>
<td>8 (3.6)</td>
</tr>
<tr>
<td>Ptosis</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>No data available</td>
<td>66 (29.7)</td>
</tr>
</tbody>
</table>
investigations yielded normal results. Brainstem and mesencephalic lesions were reported in two (75,79) of five reports on the basis of magnetic resonance imaging.

**COURSE OF THE DISEASE**

The prognosis of Miller Fisher syndrome was generally good, with recovery after a mean of 10.1 weeks. The shortest interval to remission was 14 days; the longest, 18 months. Frequent residual symptoms were hyporeflexia or areflexia (n = 36; 16.1%). The other 2 cardinal symptoms of ataxia and ophthalmoplegia persisted in 11 patients (4.9%). Both ataxia and diplopia were usually mild and did not interfere with the activities of daily life. Other persisting symptoms (n = 16; 7.2%) were psychic changes (n = 4), facial weakness (n = 4), and extrapyramidal symptoms such as tremor (n = 3). Most patients showed a complete remission without any residual symptoms (n = 119; 53.4%). There are no data about the course of the disease for 30 patients (13.5%).

Recidivism has been reported for seven patients (15,19,23,25,38,64,69,88), the disease-free interval being 1 (69) to 29 years (64). The course of the relapse was as benign as the first episode in all cases.

Eight patients died during the course of the disease (13,14,16,17,20,28,38,57,89). Secondary infections (pneumonia, sepsis) were the cause of death in four patients. One patient died because of a pulmonary embolism (17). Autopsy findings were reported for six patients. Inflammatory lesions in the brainstem were described by Al-Din (17), Bickerstaff (20), and Bignami and Servi (28). Dchaene et al. (13) found demyelination of the cranial nerves with chromatolysis of the mesencephalon. Similar findings with involvement of anterior horn cells were reported by Gronnet and Lubon (14). In the case report by Phillips et al. (16), segmental demyelination of the oculomotor nerves was the only pathological finding at autopsy. In the last three reports mentioned, there were no changes in the brainstem. None of the autopsy reports showed inflammatory lesions in the cerebellum. Some loss of Purkinje cells was described by Bignami and Servi (28).

Data about treatment in Miller Fisher syndrome are sparse. A corticosteroid therapy was established for 32 patients (14.3%). These cases did not differ from the others in terms of duration and degree of remission. Plasmapheresis was performed in seven patients: some authors (27,46,65) saw some positive effect in patients who became respiratory insufficient. In the large majority of reports no specific treatment was given, or data are missing (n = 188; 84.4%).

**THE LOCALIZATION AND NATURE OF MILLER FISHER SYNDROME**

Miller Fisher himself (12) was uncertain about the localization of the ataxia, areflexia, and ophthalmoplegia triad. Though the loss of tendon reflexes and the cerebrospinal fluid findings did make the syndrome similar to the Guillain-Barre syndrome, the striking symmetry of ophthalmoplegia with conjugate palsies during recovery and the cerebellar type of ataxia suggested, in his opinion, an involvement of the central nervous system. Weighting the different findings against each other, he concluded, "The clinical signs in question are reluctantly interpreted as manifestations of an unusual and unique disturbance of peripheral neurons." This interpretation was challenged in 1957 by Bickerstaff (20), who reported histological features suggestive of brainstem encephalitis in one of eight patients with symmetrical ophthalmoplegia and ataxia. Since then, the triad of ataxia, areflexia, and ophthalmoplegia is referred to either as Miller Fisher syndrome or as Bickerstaff encephalitis. Even in the most recent literature, the nature of this clinical entity with benign prognosis remains unclear (79,81). In general, there are three major interpretations of the nature of the Miller Fisher syndrome:

(a) The Miller Fisher syndrome is a variant of the Guillain-Barre syndrome—an idiopathic inflammation of peripheral neurons. The central nervous system-findings reported are either secondary or patients have been wrongly classified as having Miller Fisher syndrome (13,15,16,34–36,41,44,46,48,50,53,55,57,61,63,69,82,83,87,88,90).

(b) The Miller Fisher syndrome is a brainstem encephalitis without involvement of peripheral nerves. The areflexia is due to a lesion of the mesencephalon and the upper pontine reticular formation (17,20,28,29,53,59,60,74,75,81,84,85).

(c) The Miller Fisher syndrome is caused by a brainstem affection, which is accompanied by a polyneuritis (14,19,22,23,25,27,33,36,39,40,50,55,62,67,70,81,91,93).

In Table 3, we have tried to summarize both the arguments in favor of a central nervous system lesion and those suggestive of a primary peripheral disease. In fact, some of the characteristics of the Miller Fisher syndrome resemble those of Guil-
TABLE 3. Evidence of central and peripheral origin of Miller Fisher syndrome

<table>
<thead>
<tr>
<th>Central origin</th>
<th>Peripheral origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical:</td>
<td></td>
</tr>
<tr>
<td>Symmetry of ophthalmoplegia</td>
<td>Areflexia</td>
</tr>
<tr>
<td>Internuclear ophthalmoplegia or preserved convergence</td>
<td>Tetraparesis</td>
</tr>
<tr>
<td>One and a half syndrome</td>
<td>Distal sensory symptoms (arms and legs)</td>
</tr>
<tr>
<td>Convergence spasmus</td>
<td>Facial palsy of peripheral origin</td>
</tr>
<tr>
<td>Parinaud syndrome</td>
<td>Palynhesthesia</td>
</tr>
<tr>
<td>Preserved optokinetic nystagmus</td>
<td></td>
</tr>
<tr>
<td>Cerebellar ataxia</td>
<td></td>
</tr>
<tr>
<td>Facial palsy of central origin</td>
<td></td>
</tr>
<tr>
<td>Preserved Bell phenomenon</td>
<td></td>
</tr>
<tr>
<td>Hemiparesis or hemihypesthesia</td>
<td></td>
</tr>
<tr>
<td>Disturbances of consciousness</td>
<td></td>
</tr>
<tr>
<td>Epileptic fits</td>
<td></td>
</tr>
<tr>
<td>Extrapyramidal signs</td>
<td></td>
</tr>
<tr>
<td>Neurophysiological:</td>
<td></td>
</tr>
<tr>
<td>Blink reflexes</td>
<td>Electroneurography &amp; electromyography</td>
</tr>
<tr>
<td>Acoustic evoked potentials</td>
<td></td>
</tr>
<tr>
<td>EEG-slowing</td>
<td></td>
</tr>
<tr>
<td>Neuroradiology:</td>
<td></td>
</tr>
<tr>
<td>CT lesions</td>
<td>Normal CT</td>
</tr>
<tr>
<td>MRI lesions</td>
<td>Normal MRI</td>
</tr>
<tr>
<td>CSF:</td>
<td></td>
</tr>
<tr>
<td>Pleocytosis: no rise of protein</td>
<td>Albuminocytological dissociation</td>
</tr>
<tr>
<td>Neuropathological:</td>
<td></td>
</tr>
<tr>
<td>Inflammatory lesions in mesencephalon and brainstem</td>
<td>Anterior horn and bulbar chromatolysis, CN lesions</td>
</tr>
<tr>
<td>Normal findings in examination of sural nerve biopsy</td>
<td>Normal findings in brainstem and mesencephalon</td>
</tr>
</tbody>
</table>

EEG, electroencephalogram; CT, computed tomography; MRI, magnetic resonance imaging; CN, cranial nerve.

MILLER FISHER SYNDROME

lain-Barre syndrome. Both diseases frequently follow an infection, show the elevated protein value in cerebrospinal fluid, and present with pathological electrophysiological findings. However, the prognosis of the Miller Fisher syndrome is much better than that of Guillain-Barre syndrome. Irregularities in electroencephalography and computed tomography are much more common in the Miller Fisher syndrome; nor does this syndrome ever show the involvement of the autonomic system, which is typical of the Guillain-Barre syndrome.

The evidence for involvement of brainstem structures in the Miller Fisher syndrome is quite convincing. From a clinical point of view and besides the symmetry of ophthalmoplegia, the findings of internuclear ophthalmoplegia, one and a half syndrome, Parinaud syndrome, and preserved optokinetic nystagmus and Bell phenomenon in facial palsy clearly indicate a supranuclear lesion. Some neuroradiological and autopsy findings support this assumption. On the other hand, several "classical" cases showed no brainstem lesions on autopsy, and no one ever documented the cerebellar inflammation thought to be responsible for the ataxia. The affected peripheral neurons with accompanying chromatolysis of bulbar and anterior horn cells as in the Guillain-Barre syndrome were shown on autopsy several times (13,16).

On the basis of the 223 case reports analyzed, it seems improbable that the Miller Fisher syndrome is either a pure brainstem or a pure peripheral neuron disease. The different findings listed above seem to support the case for encephalomyeloneuritis. In the meantime, we have learned that in Guillain-Barre syndrome, involvement of central nervous system structures is possible. Still, the interpretation of Miller Fisher (12), which puts ataxia, areflexia, and ophthalmoplegia close to the Guillain-Barre syndrome, seems to be plausible.

Why should Miller Fisher syndrome not be a variant of the Guillain-Barre syndrome that more frequently involves the central nervous system? The benign course of this clinical entity especially speaks against the assumption of a primary inflammation of the brainstem. Some findings reported seem to be rather unusual for the Miller Fisher syndrome. They include extensor plantar response, disturbance of consciousness, cerebrospinal fluid pleocytosis, epileptic fits, severe tetraparesis of the Landry type, and respiratory insufficiency. In light of these findings, to attribute the patient's disease to Miller Fisher syndrome is a matter of debate.

CONCLUSIONS

The Miller Fisher syndrome is an idiopathic disease presenting symptoms of ataxia, areflexia, and ophthalmoplegia. It occurs most frequently in the
fifth decade of life and affects men twice as often as women. It has a subacute development after some viral infection of the respiratory tract and shows complete remission after an average 10 weeks in the majority of cases. The diagnosis of Miller Fisher syndrome should be restricted to patients with ataxia, areflexia, and ophthalmoplegia and no other severe neurologic signs. Cerebrospinal fluid studies should be normal or demonstrate some degree of elevated protein value. The main differential diagnoses are Wernicke encephalopathy, vascular brainstem disease, sinus thrombosis, multiple sclerosis, specific inflammations like diphtheria and botulism, and intracranial neoplasms (12, 17, 20, 43, 50, 55, 62-64, 93-97). Besides cerebrospinal fluid analysis, magnetic resonance imaging seems to be a mandatory test to confirm diagnosis. However, if the classical triad is present, no other investigations are necessary. From the scientific point of view, systematic magnetic resonance imaging studies in the Miller Fisher syndrome in correlation with clinical course and cerebrospinal fluid findings are desirable. Even after 35 years, the considerations of Miller Fisher prove to be justified such that this clinical entity deserves to be named for its first describer.

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MILLER FISHER SYNDROME

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It is an unnatural instinct for a neuro-ophtalmologist to pull a textbook reviewing electrodiagnostic testing of the visual system off of the library bookshelf. However, Drs. Carr and Siegel have convinced me that a walk down an electrodiagnostic pathway can be very interesting and, in fact, critical in diagnosis of neuro-ophtalmologic problems.

The authors have organized this textbook into three sections, the first being basic concepts and methods of using the electroretinogram (ERG), various types of ERG, as well as the use of visual-evoked cortical potentials. The second section is directly related to clinical applications, with thorough discussions of various types of retinopathies, their clinical presentation and the use of electrodiagnostic testing to aid in diagnosis. The last section is a very helpful but technical collection of appendices reviewing technical data of the ERG, as well as color vision testing.

I have never read a more direct and concise approach to the clinical applications of electroretinography, including specific discussions on the focal and pattern ERG. What I particularly liked were the clinical cases that were presented in association with their accompanying electroretinogram findings. The authors did a very good job in the clinical section of the book in not only reviewing the electrodiagnostic characteristics of specific retinal diseases, but also the typical presentations of funduscopic appearance. Although the photographs were not in color, they were quite characteristic of each disease process.

Although I am not a big fan of the usage of visual-evoked cortical potentials, I found the authors to be quite fair in their assessment of this particular test, and in general I agreed with their use in a clinical setting of the VEP. Although most clinicians do not actually perform the ERGs and VEPs themselves, after reading this textbook, one will become convinced that it is critical to review each wave-form yourself to be sure the interpretation is correct for your particular clinical setting.

In summary, I think Drs. Carr and Siegel have written a very concise, thorough, and interesting book that is quite clinically oriented concerning the practical use of electrodiagnostic testing of both the retina and optic nerve. It is high on my list of recommended reading and should be readily available as a reference text on the true usefulness of the ERG and VEP.

Bradley K. Farris, M.D.
University of Oklahoma
Department of Medicine
Dean A. McGee Eye Institute
Oklahoma City, Oklahoma


This book provides an excellent pictorial review of every conceivable intraocular and orbital pathological process as viewed with magnetic resonance imaging (MRI), computerized axial tomography (CT), and ultrasonography. Although somewhat redundant in the MRI and CAT scan discussions of orbital and ocular anatomy provided in different chapters, the discussions do give an excellent review of basic normal anatomy as compared to pathological processes. The textbook is broken down into separate chapters for MRI of ocular anatomy, orbital anatomy, ocular pathology, and orbital pathology, as well as its CT counterparts. There is also a nice chapter on ocular and orbital sonography. I think all of the contributing authors have done a good job in providing extensive review of all types of ocular and orbital pathology and their illustrated appearance on any of these three radiologic techniques.

This textbook should not be considered a guide or an algorithm in the clinical work-up and pursuit of neuroradiologic studies for a specific disease entity. It is more a collection of excellent illustrated examples of what certain types of ocular and orbital pathology look like when viewed with MRI, CT, or ultrasound techniques. I am not sure it was the intent of the authors to direct the reader as to

It is an unnatural instinct for a neuro-ophthalmologist to pull a textbook reviewing electrodiagnostic testing of the visual system off of the library bookshelf. However, Drs. Carr and Siegel have convinced me that a walk down an electrodiagnostic pathway can be very interesting and, in fact, critical in diagnosis of neuro-ophthalmologic problems.

The authors have organized this textbook into three sections, the first being basic concepts and methods of using the electroretinogram (ERG), various types of ERG, as well as the use of visual-evoked cortical potentials. The second section is directly related to clinical applications, with thorough discussions of various types of retinopathies, their clinical presentation and the use of electrodiagnostic testing to aid in diagnosis. The last section is a very helpful but technical collection of appendices reviewing technical data of the ERG, as well as color vision testing.

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In summary, I think Drs. Carr and Siegel have written a very concise, thorough, and interesting book that is quite clinically oriented concerning the practical use of electrodiagnostic testing of both the retina and optic nerve. It is high on my list of recommended reading and should be readily available as a reference text on the true usefulness of the ERG and VEP.

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This textbook should not be considered a guide or an algorithm in the clinical work-up and pursuit of neuroradiologic studies for a specific disease entity. It is more a collection of excellent illustrated examples of what certain types of ocular and orbital pathology look like when viewed with MRI, CT, or ultrasound techniques. I am not sure it was the intent of the authors to direct the reader as to
what type of neuroradiologic technique would be most favorable for a specific disease entity, and it certainly was not clear after reading the book. In addition, although the figures were quite clear and excellent, it would have helped orient the reader to have right and left designation on each scan. Conspicuous by its absence was a discussion of ultrasound of optic nerve edema, including the 30-degree text, as well as the extensive use of the MRI in demyelinating states and optic neuritis. On the other hand, there was an overabundance of excellent illustrations on nonspecific orbital inflammatory diseases, but fewer on thyroid eye disease.

Aside from those minor complaints, when this textbook is used as an excellent source of illustrative appearances of a multitude of disease processes, it is most valuable. I particularly liked the MRI and CT discussions on orbital and ocular trauma. I think the reader will not only enjoy the photographic illustrations of the various neuroradiologic pictures, but also the excellent clinico-pathological discussions of each disease process aside from its neuroradiologic appearance.

Bradley K. Farris, M.D.
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Literature Abstracts


This intriguing technique seeks to objectively assess a patient’s visual field based on differential pupil responses with light shown at different parts of the retina. The actual plots obtained look surprisingly like a conventional visual field but can be obtained very quickly (5 minutes versus 20 minutes for an automated visual field) and are not dependent on a patient’s subjective response, although alertness, good fixation, and non-miotic pupils are necessary. The discussion by Dr. Richard Mills highlights the exciting possibilities of this kind of perimetry while also recognizing the current problems.

Lyn A. Sedwick, M.D.


This letter to the editor documents yet another case of a large-cell lymphoma of the orbit in a patient with AIDS.

Lyn A. Sedwick, M.D.

Immunosuppressive Drugs in Immune and Inflammatory Ocular Disease. Hemady R, Tauber L, Foster CS. *Surv Ophthalmol* 1991;35:369-85 (Mar-Apr). [Reprint requests to Dr. C. S. Foster, Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, MA 02114.]

In this article, specific immunosuppressive drugs (cyclophosphamide, chlorambucil, methotrexate, azathioprine, cyclosporine A, bromocriptine, dapsone, and colchicine) are discussed. Their modes of action, indications for ophthalmologic disease, dosages, and side effects are discussed. They seem most accepted for uveitis, scleritis, and orbital inflammatory disease, although some have very specific use (i.e., bromocriptine for pituitary adenoma and Parkinson’s disease).

Lyn A. Sedwick, M.D.


An unfortunate 15-year-old boy underwent embolization of the left internal maxillary artery to control traumatic epistaxis and had unplanned embolization of the ophthalmic artery. In retrospect, choroidal blush could be seen on arteriography of the external carotid, which indicated anastomosis between the external carotid and posterior ciliary arteries via the lacrimal artery. If this rare anastomosis is detected before embolization, caution can be used; however, the patient must be advised of the risk of permanent visual loss.

Lyn A. Sedwick, M.D.


Drs. Petitto and Buckley report their experience using botulism in 20 patients with strabismus following retinal detachment surgery. In their patients, 85% achieved fusion, with 73% requiring only one or two injections. Discussion by Dr. John Lee adds other similar cases, and he concludes that
this is a safe and effective treatment option in such cases.

Lyn A. Sedwick, M.D.


The authors present 10 patients with acute idiopathic blind spot enlargement who had no disc edema. Only 3 patients had multiple evanescent white dot syndrome, and 1 had an acute macular neuroretinopathy. The authors propose that multiple evanescent white dot syndrome is a subset of acute idiopathic big blind spot syndrome, not vice versa, as has been previously proposed.

Lyn A. Sedwick, M.D.


These articles describe a new technology for orbital vascular imaging and show the utility of the testing in carotid cavernous fistula, superior ophthalmic vein thrombosis, and internal carotid artery occlusion. The transducer probe rests on closed eyelids; structures with blood flow toward the probe appear red (arterial) and away from the probe appear blue (venous). In carotid cavernous fistula, the superior ophthalmic vein appears enlarged and red, indicating the abnormal arterialized blood flow. In superior ophthalmic vein thrombosis, the vein is also enlarged but is blue, and other orbital veins show reversal of flow from shunting. The color Doppler pictures are very clear and easy to understand. This is an interesting technology that may save patients from more invasive vascular studies.

Lyn A. Sedwick, M.D.


Three patients are presented with scotomatous central, peripheral, and macular sparing and bilateral peripheral homonymous hemianopic defects from magnetic resonance imaged occipital lobe lesions. The authors use these data to revise the classic Holmes map of the presumed field representation of the primary visual cortex in favor of increased central and decreased peripheral representation.

Lyn A. Sedwick, M.D.

Primary Orbital Intraosseous Hemangioma. Relf SJ, Bartley GB, Unni KK. Ophthalmology 1991;98:541-7 (Apr). [Reprint requests to Dr. G. B. Bartley, Department of Ophthalmology, Mayo Clinic, 200 First Street, S.W., Rochester, MN 55905.]
Five patients with intraosseous hemangioma of the orbit are presented, and the literature on this rare tumor reviewed. Discussion by Dr. Hans Grossniklaus includes a warning to consider this tumor when operating on orbital bone lesions and to be prepared for difficulty with hemostasis.

Lyn A. Sedwick, M.D.


The authors report successful treatment of a superior orbit eosinophilic granuloma in a 17-year-old with intralesional steroid injection with computerized tomographic monitoring during the procedure.

Lyn A. Sedwick, M.D.


This photo essay gives nice pictures of the patient, scans, surgery, and pathologic sections of an orbital chloroma.

Lyn A. Sedwick, M.D.


An 83-year-old lady with known mycosis fungoides, mainly on her lower extremities, developed diplopia and a red eye. She was found to have orbital mycosis fungoides.

Lyn A. Sedwick, M.D.


A 4-year-old girl with congenital oculomotor nerve palsy could elevate her ptotic lid by contracting the platysma muscle. The author notes that facial nerve misdirection to the levator has not previously been described.

Lyn A. Sedwick, M.D.


The authors reviewed records of 45 patients with nonarteritic ischemic optic neuropathy and compared these to age-matched controls. No excess correlation to increased intraocular pressure in patients with ischemic optic neuropathy versus controls was found.

Lyn A. Sedwick, M.D.

Sector Palsy of the Sphincter Pupillae Muscle After Argon Laser Trabeculoplasty. Pfeiffer N, Kommerell G. Am J Ophthalmol 1991;111:511-2 (Apr). [Inquiries to Dr. N. Pfeiffer, University Eye Hospital, Langenbeckstr. 1, D-6500, Mainz, Germany.]

A patient sustained a sectoral palsy of pupil constriction immediately following argon laser trabeculoplasty that normalized after 15 months. The authors postulate that a parasympathetic loop of fibers was hit by the laser near the trabecular meshwork leading to the pupil anomaly.

Lyn A. Sedwick, M.D.

Scleritis and Wegener's Granulomatosis in Children. Sacks RD, Stock EL, Crawford SE, Greenland MJ, O'Grady RB. Am J Ophthalmol 1991;111:430-3 (Apr). [Reprint requests to Dr. E. L. Stock, 303 E. Chicago Avenue, Department of Ophthalmology, Northwestern University Medical School, Chicago, IL 60611.]

Scleritis and Wegener's Granulomatosis in Children.
Two young teenagers with acute scleritis were found to have Wegener's granulomatosis, based on sinus biopsy in one and lung biopsy in the other.

Lyn A. Sedwick, M.D.


The authors review eight patients with congenital homonymous hemianopia. All had computerized tomography, and the three with normal computerized tomography had magnetic resonance imaging that showed visual radiation abnormality in two and absence of the optic tract in one. The two with visual radiation damage only on magnetic resonance imaging were studied with positron emission tomography and found to have normal resting glucose metabolism in both occipital lobes but no increase in activity in the occipital cortex corresponding to the homonymous hemianopia with whole field stimulation.

Lyn A. Sedwick, M.D.


A 3-month-old boy with bilateral oculomotor nerve palsy was found to have a brain anomaly in the region of the basal ganglia. One pupil was normal and there was no evidence of aberrant regeneration. The authors conclude that the origin of the oculomotor nerve palsies was central and developmental in this case, and that the normal pupil reflected the later development of the Edinger-Westphal nucleus on one side.

Lyn A. Sedwick, M.D.

**A Magnetic Resonance Imaging Study of the Upshoot-Downshoot Phenomenon of Duane's Retractive Syndrome.** Bloom JN, Graviss ER, Mardelli PG. *Am J Ophthalmol* 1991;111:548-54 (May). [Reprint requests to Dr. J. N. Bloom, Bethesda Eye Institute, St. Louis University School of Medicine, 3655 Vista Avenue, St. Louis, MO 63110.]

Two patients with Duane's retraction syndrome were examined with orbital magnetic resonance imaging. The authors studied each eye's muscle and optic nerve positions in primary position and in adduction, where one patient had an upshoot and the other a downshoot of the affected eye. They found no significant displacement of the lateral rectus muscle with up- or downshoot which makes unlikely the theory that these overshoots result from a slippage of this muscle vertically in adduction to produce the vertical eye movement.

Lyn A. Sedwick, M.D.


The perils of perimetry! A patient undergoing automated perimetry, with inadvertent hyperextension of his neck, suffered transient symptoms of vertebral artery occlusion following the testing. The perimetry position was felt to be causative and the authors recommend "instructing clinical personnel about the potential hazards of neck hyperextension."

Lyn A. Sedwick, M.D.

**Associated Neurologic and Ophthalmologic Findings in Congenital Oculomotor Nerve Palsy.** Hamed LM. *Ophthalmology* 1991;98:708-14 (May). [Reprint requests to Dr. L. M. Hamed, University of Florida College of Medicine, Department of Ophthalmology, Box J-284, JHMHC, Gainesville, FL 32610-0284.]
In this series of 14 patients with congenital oculomotor nerve palsy, 10 had associated neurological disorders. Details of these cases are well presented and compared to the other reported cases.

**Lyn A. Sedwick, M.D.**

**Late Recovery of Function After Oculomotor Nerve Palsy.** Golnik KC, Miller NR. *Am J Ophthalmol* 1991;111:566-70 (May). [Reprint requests to Dr. N. R. Miller, Johns Hopkins Hospital, Wilmer Eye Institute, 600 N. Wolfe Street, Maumenee Bldg., Rm. B-109, Baltimore, MD 21205.]

Three patients with differing etiologies for oculomotor nerve palsy (orbital trauma, orbital hemorrhage, pituitary apoplexy) had late improvement in ocular motility, i.e. 2 or 3+ years post insult. All had months to years of stability before this improvement occurred. Perhaps the common recommendation for eye muscle surgery after 6 months to a year of stable measurement should be reconsidered.

**Lyn A. Sedwick, M.D.**

**Cilioretinal Artery Occlusion in Young Adults with Central Retinal Vein Occlusion.** Schatz H, Fong ACO, McDonald HR, Johnson RN, Joffe L, Wilkinson CP, de Laey JJ, Yannuzzi LA, Wendel RT, Joondeph BC, Angioletti LV, Meredith TA. *Ophthalmology* 1991;98:594-601 (May). [Reprint requests to Dr. H. Schatz, 1 Daniel Burnham Court, Suite 210, San Francisco, CA 94109.]

The authors report 10 patients, aged 23-44 years, with a picture of central retinal vein occlusion and cilioretinal artery occlusion. In most, good visual function was eventually recovered. The authors discuss the etiology of these “mild” cilioretinal artery occlusions and Dr. Orth comments on the paper and other relevant literature in his discussion following it.

**Lyn A. Sedwick, M.D.**


The first article, a “mega-article” of twelve pages, describes 49 cases of Leber’s optic neuropathy with a mitochondrial DNA mutation at position 11778 (testing with Sfa N1 restriction endonuclease was positive in all; most cases were “confirmed” by testing with Mae 3 restriction enzyme). About half of the cases had no identifiable relative in the maternal line with symptoms of Leber’s, but about half did. The clinical characteristics of their cases are presented in detailed fashion and compared to other reported groups of patients with Leber’s.

The second article is an overview of mitochondrial DNA ocular disease, specifically Leber’s and Kearns-Sayre, in terms of specifics of the genetics involved. Interestingly—and important to remember with restriction enzymes Sfa N1 and Mae 3 (which are discussed in fascinating basic-science detail)—only about 50% of cases and families of clinical Leber’s will have positive endonuclease testing, presumably because a different subunit of mitochondrial DNA also coding for a different but also crucial part of the respiratory enzyme NADH can produce Leber’s.

**Lyn A. Sedwick, M.D.**


Two patients with this unusual disease are described in whom there were prominent orbital findings—proptosis, lid retraction, and/or ophthalmoplegia. This idiopathic condition causes inflamma-
tion of a variety of tissues with a fibrotic process, including orbital tissue in these patients. Clinically and radiographically, these patients' conditions could easily be confused with thyroid eye disease, orbital pseudotumor, metastatic carcinoma or lymphoma, as the authors point out in their discussion.

Lyn A. Sedwick, M.D.


This clinical pathologic correlation presents a young alcoholic woman with bilateral subacute visual loss. All discussants agree on the diagnosis (nutritional amblyopia, tobacco-alcohol amblyopia) and the differential diagnosis. The treatment advised varies somewhat among the discussants, however. This is such a nice neuro-ophthalmic disease, as the visual loss can be very significantly reversed with recognition and therapy.

Lyn A. Sedwick, M.D.

Brown Tumor and Secondary Hyperparathyroidism.

A patient with chronic renal failure developed proptosis and diplopia. Computerized tomographic scanning showed a left frontal-ethmoid sinus tumor extending into the superonasal orbit. This Brown tumor, which was a result of secondary hyperparathyroidism in this patient with renal failure, was totally resected. Five previously reported cases are reviewed.

Lyn A. Sedwick, M.D.

Optic Nerve Sheath Decompression for Nonarteritic Ischemic Optic Neuropathy Improves Multiple Visual Function Measurements.

Optic Nerve Sheath Decompression for the Treatment of Progressive Nonarteritic Ischemic Optic Neuropathy.
Spoor TC, Wilkinson MJ, Ramocki JM. Am J Ophthalmol 1991;111:724-8 (June). [Reprint requests to Dr. T. C. Spoor, Kresge Eye Institute, Wayne State University, 4717 Saint Antoine, Detroit, MI 48201.]

Two more articles regarding optic nerve sheath decompression for ischemic optic neuropathy, the first involving seven patients, five with progressive non-arteritic ischemic optic neuropathy (NAION) and two with nonprogressive NAION, and the second article reporting decompression in four patients, five eyes, with progressive NAION. In the first study, all patients had some increase in visual acuity, although it was only slight in one and only one achieved better than 20/100, and most had improvement in visual field. In the second study, three eyes improved postoperatively to 20/25 (as well as one fellow eye improving from 20/200 to 20/25) with improved visual fields. As one reads these articles and reviews Sergott's original article in the December 1989 Archives of Ophthalmology, it becomes apparent that in order to fully evaluate these results, current studies demonstrating that progressive or nonprogressive NAION has a uniformly poor outcome (an assumption you must make to subject a patient to optic nerve sheath decompression) would be invaluable. Also, the way in which patients are selected for these trials (i.e., how long from initial onset is "progressive") and outcome is judged (e.g., visual improvement immediately postoperatively in some versus not until several weeks later in others) confounds interpretation of the data. Optic nerve sheath decompression seems to be a useful therapy for selected patients, but it would be very helpful to see some prospective or retrospective studies of large series of patients with NAION to know what the natural history of this disease is before deciding whether optic nerve sheath decompression is a valid alternative.

Lyn A. Sedwick, M.D.

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Lyn A. Sedwick, M.D.

Transient Cranial Nerve Palsies After Cavernous Sinus Fistula Embolization.
Sabates FN Jr., Tsai F, Sabates NR, Blitstein B. Am J Ophthalmol 1991;111:771-3 (June). [Inquiries to Dr. F. N. Sabates, Jr.,
A patient treated with balloon embolization of a traumatic carotid cavernous fistula developed third, fourth, and sixth nerve palsies same side 9 days postoperatively. It was postulated that the balloons, containing contrast medium of increased osmolarity compared to serum, had increased in size on scan and lowering serum osmolarity cleared the palsies with decrease in the size of the balloons.

Lyn A. Sedwick, M.D.


The authors report magnetic resonance imaging characteristics in four patients with neurofibromatosis 1 and optic nerve glioma, which they believe may be typical of optic nerve gliomas in this disease.

Lyn A. Sedwick, M.D.

Leptomeningeal Dissemination of Optic Pathway Gliomas in Three Children. Bruggers CS, Friedman HS, Phillips PC, Wiener MD, Hockenberger B, Oakes WJ, Buckley EG. Am J Ophthalmol 1991;111:719-23 (June). [Reprint requests to Dr. C. S. Bruggers, P.O. Box 2916, Pediatric Hematology-Oncology, Duke University Medical Center, Durham, NC 27710.]

The authors report three children, aged 8 years, 14 weeks, and 2 years, who presented with optic pathway glioma. Two had leptomeningeal metastases at onset; one developed these after surgical biopsy and radiation therapy. Although a grave complication, the authors note that leptomeningeal metastases are rare with these tumors.

Lyn A. Sedwick, M.D.


Following left retrobulbar injection for cataract surgery, the patient had uncontrolled shivering and subsequent total ophthalmoparesis of the other eye, which resolved in 1 hour. The authors discuss why they think this probably resulted from inadvertent orbital vein injection and secondary involvement of the cavernous sinuses.

Lyn A. Sedwick, M.D.
To the Editor:

We read with interest the article by Hriso and colleague (1) who presented a patient with monocular elevation paresis and incomplete ptosis due to midbrain infarction involving the fascicular segment of the oculomotor nerve. Based on previously reported cases of complete and partial oculomotor nerve palsies (2-5), we proposed (6) that the transverse oculomotor fascicular arrangement in the ventral midbrain tegmentum from lateral to medial was as follows: inferior oblique fascicles; superior rectus fascicles; medial rectus and levator palpebrae (lid) fascicles; inferior rectus fascicles; and most medially, the pupillary fibers. The cases that were available at the time of that report were insufficient to determine whether the lid fascicles were intermediate between the medial rectus and inferior rectus fascicles or possibly positioned between the superior rectus and medial rectus fascicles (6). The case by Hriso and colleague documented the presence of inferior oblique, superior rectus, and levator palpebrae paresis, with simultaneous sparing of medial rectus function. Their case and two other similar cases (7) would favor the latter conclusion that the levator palpebrae fascicles are in an intermediate location between the superior rectus and medial rectus fascicles. The availability of such clinical cases has helped to advance our understanding of the transverse neuroanatomic organization of the fascicular fibers of the oculomotor nerve (6). Future clinicopathologic correlation is awaited.

Acknowledgment: This research was aided in part by an unrestricted grant from Research to Prevent Blindness.

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REFERENCES


To the Editor:

We read with interest the article by Smith et al. (1) concerning a case of Leber's hereditary optic neuropathy with bilateral distended optic nerve sheaths. Optic nerve sheath decompression performed 8 months after onset of visual loss did not improve visual acuity. The authors were unaware of any previous cases of Leber's with distended optic nerve sheaths and questioned whether earlier intervention in such a case would be efficacious. We report a similar case in which optic nerve sheath decompression was performed 1 month after the onset of visual loss.

Report of a case. A 19-year-old man with previously normal vision had sudden onset of reduced vision in his right eye in late November, 1990, followed by a similar episode in the left eye one month later. He had a family history of Leber's hereditary optic neuropathy in a maternal cousin and uncle. He was treated with oral prednisone for 2 weeks with no improvement. A computerized tomography (CT) scan on January 4, 1991, was read as normal.

Examination at University of Alabama at Birmingham on January 9, 1991 revealed visual acuity of 5/200 right eye and 20/400 left eye. There was no afferent pupillary defect. Color vision was reduced bilaterally. Slit-lamp exam was normal. Ophthalmoscopy showed clear media with mild temporal pallor of the right disc and minimal peripapillary telangiectatic vessels on the left. Visual fields demonstrated bilateral central scotomas. Fluorescein angiography showed no leakage from the discs or peripapillary vessels. Blood sent for mitochondrial...
DNA studies was positive for the Wallace 11778 point mutation. An electrocardiogram revealed a right bundle branch block.

The CT scan was reviewed and the intraorbital segments of each optic nerve appeared enlarged (Fig. 1). Quantitative ultrasonography showed both optic nerve sheaths to be distended. The difference in neural and dural diameters was 1.90 mm on the right and 1.80 mm on the left. The upper left of normal is 1.50 mm in this laboratory. The optic nerve proper was also slightly enlarged in each eye.

An optic nerve sheath decompression through a medial approach was performed on the left eye on January 25, 1991. At surgery, the optic nerve sheath appeared mildly distended and as incisions were made there was prompt release of cerebrospinal fluid.

Orbital ultrasonography done on February 7, 1991, showed no change in the size of the left optic nerve, but the difference in neural and dural diameters decreased to 1.50 mm. The perineural space decreased slightly on the right to 1.78 mm; however, this difference of 0.12 mm. from the preoperative exam was too small to be considered a definite decrease. Unfortunately, the vision did not improve following the procedure. The patient was last seen March 6, 1991, with vision remaining 5/200 on the right and 20/400 on the left. Both optic discs showed temporal pallor, the right more than the left. There was no improvement in visual fields.

Comment: Optic nerve sheath decompression was performed 1 month after visual loss in this patient with Leber's hereditary optic neuropathy. Although ultrasonography demonstrated reduction of the perineural space to normal limits, there was no improvement in visual function. The cause of the sheath distension, and its effect, if any, on optic nerve function is uncertain. Further evaluation is needed to determine if early optic nerve sheath decompression is of any benefit in cases of Leber's hereditary optic neuropathy.

REFERENCE


Douglas R. Wilson, M.D.
Lanning B. Kline, M.D.
Department of Ophthalmology
University of Alabama School of Medicine
Birmingham, Alabama

To The Editor:

I suppose all of us believe that our technique for doing superficial temporal artery biopsies is the best. The technique described by Dr. Tomsak in the Journal of Clinical Neuro-ophthalmology 1991;11(3):202-204 was so opposed to what I have taught my students I felt it necessary to reexamine what I had been doing. I conclude that there are some problems with what he suggests.

Early in my practice I encountered two patients who had had superficial temporal artery biopsies by general surgeons in the location described in his article. Both of these patients had painful masses under the scar, which we assumed were neuromas. I think that the problem is that the site suggested by Dr. Tomsak is a bit crowded. As he mentions, the superficial temporal vein lies next to the artery in front of the ear. Also, a branch of the auriculotemporal nerve usually lies directly on the artery in this region.

I am sure that Dr. Tomsak is a careful surgeon who can dissect the vein and nerve free without any damage. It seems to me, however, to be a lot of work for the routine case and perhaps in less experienced hands, a somewhat more dangerous procedure than a biopsy done more peripherally.

Don C. Bienfang, M.D.
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Announcements

The Neurology Department of the Miami Children's Hospital will offer the Thirteenth Annual Child Neurology Postgraduate Course, June 11-13, 1992, at the Sonesta Beach Hotel, Key Biscayne, Florida. The accreditation for the course is 16 hours in AMA Category I. Topics will include neonatal neurology, developmental disorders, and neuromuscular diseases and seizures. Guest faculty will include Drs. A. Bellman, L. Baumbach, H. Chugani, S. Moshe, T. Naidich, W. Peacock, E. S. Roach, and S. Swedo. For more information, contact Dr. Oscar Papazian, Miami Children's Hospital, Department of Neurology, 3200 S.W. 60th Court, Miami, Florida 33155; telephone (305)662-8330; FAX (305)663-2813.


The Fight for Sight Research Division of the National Society to Prevent Blindness is pleased to announce the awards program for 1992-93. The program includes Grants-in-Aid fund studies of priority interest and pilot projects with a maximum annual award of $12,000; Postdoctoral Fellowships with a maximum annual award of $14,000; and Student Fellowships for summer research with awards of $500 per month for a maximum of three months. The closing date for receipt of applications for 1992-93 is March 1, 1992. Application forms and brochures are available from the Fight for Sight Research Division of the National Society to Prevent Blindness, 500 East Remington Road, Schaumburg, Illinois 60173.