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Acute Zonal Occult Outer Retinopathy

Donders Lecture: The Netherlands Ophthalmological Society, Maastricht, Holland, June 19, 1992

J. Donald M. Gass, M.D.

Purpose: This report describes 13 patients, predominantly young women, with a syndrome characterized by rapid loss of one or more large zones of outer retinal function, photopsia, minimal fundus changes, and electroretinographic abnormalities affecting one or both eyes. All patients on follow-up examination had persistent visual field defects, and most had chronic photopsia and zones of pigment epithelial atrophy. Evidence is presented that these patients probably represent part of the spectrum of a single disorder that includes the multiple evanescent white-dot syndrome (MEWDS), acute idiopathic blind-spot-enlargement syndrome (AIBSES), acute macular neuroretinopathy (AMN), and the pseudo-preserved ocular histoplasmosis syndrome (P-POHS).

Methods: The medical records of these 13 patients and 2 additional patients, who developed, in addition to the features of this syndrome, funduscopic changes typical of MEWDS, AMN, and P-POHS, were reviewed and follow-up obtained. Results: These patients had extensive unrewarding medical and neurological investigations because of suspected diagnoses, including central nervous system disorders, cancer-associated retinopathy, retinal vasculitis, diffuse unilateral subacute neuroretinitis, and tapetoretinal degenerations. Although most patients retained good visual acuity, all had permanent visual field loss that in some cases was severe. The cause of the disorder was not determined. No effective treatment was found. Conclusions: Acute visual loss and photopsia in these patients is probably caused by damage to large zones of the outer retina that appears unaffected ophthalmoscopically. Electroretinography is important in early diagnosis. Future investigations probably will reveal further evidence linking this disorder to MEWDS, AIBSES, AMN, and P-POHS.

Key Words: Scotomata—Photopsia—Electroretinography.

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This report concerns a clinical syndrome characterized by (a) acute loss of one or more zones of outer retinal function, involving one or both eyes of predominantly young women, usually associated with photopsia, (b) minimal or no fundus changes initially, (c) electroretinographic abnormalities, and (d) permanent visual field loss that is often associated with late development of fundus changes. These patients were subjected to extensive medical and neurological investigations because of suspected optic neuritis, central nervous system disorders, retinal vasculitis, cancer-associated retinopathy, and tapetoretinal dystrophy.

The purpose of this report is to present evidence that these patients represent part of the spectrum of what probably is a single disease, that includes the multiple evanescent white-dot syndrome, acute idiopathic blind-spot-enlargement syndrome, acute macular neuroretinopathy, and the pseudo-preserved ocular histoplasmosis syndrome. Acute zonal occult outer retinopathy is suggested as an appropriate name for this disorder.

METHODS AND MATERIALS

Since 1986 I have examined 10 patients and followed by mail consultation 3 other patients with the aforementioned syndrome. All patients had complete eye examinations that included fundus photography, fluorescein angiography, and electroretinography. All had medical consultation, and all but one had neurological consultation that included at least the following: magnetic resonance imaging or computed tomography, brain scan, chest radiography, routine blood counts, sedimentation rate, blood chemistries, ANA, rheumatoid factor, RPR, and FTA-ABS. Three had serologic analysis for antibodies to retinal proteins (retinal S antigen, rhodopsin, interreceptor binding protein,
and cancer-associated antigen) by Dr. C. E. Thirkill. All patients were followed for 6 to 71 months (mean: 33 months; median: 27 months). No patient meeting the selection criteria was lost to follow-up.

To demonstrate the interrelationship between these patients and those previously reported as having the multiple evanescent white-dot syndrome, acute idiopathic blind-spot-enlargement syndrome, acute macular neuroretinopathy, and the pseudo-presumed ocular histoplasmosis syndromes, two additional case reports (Cases 14 and 15) are presented. Details of the early clinical course of one (Case 14) have been previously reported (1).

CASE REPORTS

Case 1

In June 1986, a 29-year-old female nurse noted a large scotoma associated with the acute onset of "a blue light, iridescent flash, and shimmering heat wave" involving the superonasal visual field of the right eye. Examination by several ophthalmologists revealed visual acuity of 20/20 in both eyes, vitreous cells in the right eye, normal fundi, and a dense peripheral superonasal visual field defect in the right eye (Fig. 1). Neurological examination and investigations, including visual evoked response, complement C3, C4, CH 1100, serum electrolytes, and angiotensin-converting enzyme were negative. HLA B27 assay was positive. One month later, she developed a zone of pigment epithelial depigmentation and focal venous sheathing in the inferotemporal quadrant of the right fundus (Fig. 2). During the subsequent 6 years she was bothered by the photopsia and the field defect, both of which were accentuated by bright light, upper respiratory infections, and fatigue. Although she believed that the scotoma in the right eye had enlarged somewhat, serial visual fields showed no change. At last examination her visual acuity was 20/20 bilaterally, and the fundi were unchanged except for intraretinal migration of pigment within the depigmented zone inferotemporally in the right eye and several focal areas of perivenous sheathing in the retina of the left eye nasally. Color vision (Hardy-Rand-Rittler plates) testing was normal in both eyes. Electroretinography revealed subnormal rod and cone amplitudes in the right eye. Electrooculography showed a reduced response in the right eye (Arden ratio: 1.71 right eye, 2.68 left eye).

Case 2

In September 1988, a 13-year-old girl noted a large temporal scotoma in the right eye. Initial examination by her optometrist revealed no explanation for her complaints. She was referred to a retinal specialist in April 1989. Her visual acuity at that time was 20/30 right eye, 20/20 left eye. There was a dense scotoma temporally and inferiorly on Amsler grid testing and to finger-counting in the right eye. Ophthalmoscopic examination revealed a large, sharply defined 12 × 15 mm zone of mild depigmentation of the pigment epithelium involving the juxtapapillary area extending into the midperiphery nasally. There were 1+ vitreous cells in the right eye. Fluorescein angiography showed the large zone of depigmentation in the right eye. It was normal in the left eye. Electroretinographic examination revealed reduced rod and cone amplitudes and delayed responses in the right eye.

Electrooculography showed no light rise in the right eye and was normal in the left eye. In February 1992, her examination was unchanged except for greater prominence of the pigment epithelial atrophy.

Case 3

On January 14, 1988, a healthy 25-year-old woman developed photopsia and a large central
and temporal scotoma in the right eye. Examination revealed visual acuity of 20/400 right eye, 20/20 left eye, and a + afferent pupillary defect in the right eye. Visual field examination showed a large dense central and temporal defect (Fig. 1). The fundi were normal. Retrobulbar neuritis was suspected. Neurological examination and laboratory investigations, including visual evoked potential, were normal. One month later the visual acuity was 20/200 right eye and the visual fields were unchanged. Examination of the right fundus and fluorescein angiography revealed two subtle discrete zones of pigment epithelial depigmentation. One zone was at the temporal margin of the macula, and the other large zone surrounded the optic disc and extended to the equator nasally (Fig. 3). In February 1989, an electroretinogram revealed reduced rod and moderately abnormal cone responses in the right eye. In March 1989, the visual function of both eyes was unchanged. There was no evidence of optic atrophy or abnormality in the central macular area of the right eye. Telephone follow-up in May 1992 revealed no change in symptoms.

**Case 4**

In October 1988, a 25-year-old male medical student developed "blips of burgundy and yellow
lights with amoeboid movement” in the superior visual fields of both eyes. This was followed within a few days by a large scotoma involving most of the superior visual field of both eyes. The fundi were normal. Neurological examination and laboratory investigations, including HIV titers, were normal. When examined 1 month later, his visual acuity was 20/15 in both eyes, and the visual fields were unchanged (Fig. 4). There were a few vitreous cells in the left eye. The fundi were normal. Electroretinography revealed reduced cone responses bilaterally, more so in the left eye. Over the subsequent months there was incomplete resolution of the scotomata and photopsia, but both were still present in October 1990.

Case 5

In November 1991, a healthy 33-year-old man suddenly noticed “persistent and constantly moving blue and red dots of light” and a scotoma in the inferonasal field of the left eye. Several days later he developed an inferior scotoma in the right eye. One month later his visual acuity was 20/20 bilaterally. Fundus examination and fluorescein angiography were normal. Visual field examination showed slight blind-spot enlargement bilaterally and a dense scotoma inferiorly in the right eye and nasally in the paracentral area in the left eye (Fig. 1). Neurological examination and laboratory studies including visual evoked responses, color vision testing, and Lyme Western blot were normal. In January 1992, a focal electroretinogram was abnormal in the left eye. When examined 6 months after the onset of symptoms, his visual acuity and visual fields were unchanged. There were no vitreous cells. His fundi were normal except for a subtle, 2 × 3 disc-diameter zone of depigmentation of the pigment epithelium temporal to the center of the macula in the left eye (Fig. 5).

Case 6

On July 13, 1989, a 63-year-old woman noted the abrupt onset of photopsia and a scotoma temporally in the left eye. Several years previously she had repair of a rhegmatogenous detachment in the right eye. Visual acuity in that eye did not return to normal postoperatively. Examination by her local physician and a retinal specialist failed to find a cause for her complaints. Neuro-ophtalmological and neurological consultations provided no explanation for her large dense temporal visual field defect in the left eye (Fig. 1). Studies, including cerebral arteriography and bronchoscopy, were unrevealing. Examination on July 31, 1989 revealed visual acuity 20/60 right eye and 20/30 left eye, a 1+ left afferent pupillary reaction, and 2+ vitreous cells in the left eye. Her visual fields were unchanged. Both fundi were normal except for evidence of an equatorial scleral buckle in the right eye and mild juxtapapillary pigment epithelial atrophy in both eyes. The latter was evident by fluorescein angiography that was otherwise normal. Electroretinography revealed 20% reduction in the rod and cone amplitudes in the left eye. The photo-
topsias and the scotoma lessened over the following few months. In August 1991, the visual acuity in the left eye was 20/20, there were fewer vitreous cells, and the visual field defect was smaller. In June 1992, she was still aware of the scotoma but no longer had photopsia.

Case 7

On June 8, 1989, a healthy 44-year-old airline stewardess developed a scotoma superotemporally and “an explosion of pink, white, blue, and red lights, like St. Elmo’s fire on the control panel of an airliner” in the right eye. The scotoma progressed to involve the nasal field. Examination by her local physician revealed bilateral superior visual field defects and 20/20 visual acuity (Fig. 4).

The fundi were normal. Color vision (Hardy-Rand-Rittler plates) and fluorescein angiography were normal. Neurological and medical evaluations were normal except for elevated blood pressure and hypercholesterolemia. When examined here on August 3, 1989, the visual acuity and fundi were normal. Central field examination revealed a biquadrantic superior field defect involving the blind spot in the right eye and a similar but less prominent defect in the left eye. She was asymptomatic in the left eye. Electroretinography revealed low normal amplitudes in both eyes. The cones were more affected than the rods and the right eye was more affected than the left eye. In September 1990, there was slight improvement in the visual fields. Telephone follow-up in May 1992 revealed that the scotoma and photopsia in the
right eye were unchanged. She had no symptoms in the left eye.

Case 8

On September 26, 1986 a 24-year-old woman, who was recovering from an upper respiratory infection, awoke to find she had loss of peripheral vision, photopsia, and nyctalopia in both eyes. Several days later, examination by her local ophthalmologist revealed multiple widespread dense scotomata in both eyes and normal fundi (Fig. 6). Visual acuity was 20/200 right eye and 20/20 left eye. Over the subsequent 3 weeks her vision deteriorated further, and the field defects became confluent. Her visual acuity was 20/70 right eye and 20/300 left eye. There were a few anterior chamber cells, many vitreous cells, and retinal perivenous cuffing in both eyes. Sarcoidosis was suspected but medical and neurological evaluation were negative. She was treated with oral prednisone and the visual acuity improved. By November 1986, she had developed narrowing of the retinal vessels bilaterally. Her visual evoked potential was abnormal in both eyes. Electrorretinography revealed extinguished rod responses and cone responses 10% of normal in both eyes. In March 1987, her visual acuity was 20/30 right eye and 20/40 left eye. In both eyes, there were marked visual field defects (Fig. 1), vitreous cells, retinal vessel narrowing, and attenuation of the retinal pigment epithelium that were not evident in her initial fundus photographs (Fig. 6). She missed 10 of 15 Ishihara plates with the right eye and 15 of 15 with the left eye. Over the following 4 years the pigment epithelial atrophic changes became more prominent and were associated with bone-spicule migration into the retina. Despite minimal changes in her visual fields, the patient continued to lose central vision in her left eye. At the time of last examination in April 1991, the visual acuity was 20/25 right eye and 20/200 left eye. She was still bothered by photopsia and "wormlike movements" in both eyes.

Case 9

In January 1989, a 23-year-old woman noted floaters, photopsia, and, within several months, an inferior scotoma that soon extended to involve the superior visual field in the left eye. Around 18
months previously she had had infectious mono-nucleosis and chronic fatigue thereafter. In April 1989, a retinal specialist noted mild swelling of the left optic disc and slight narrowing of the retinal arteries. Visual field examination revealed a marked loss of the peripheral field in the left eye (Fig. 4). The visual field was normal in the right eye. Neurological and rheumatological evaluations, including lumbar puncture and complement C3/C4, were normal, except for an ANA of 1:2560. A several weeks course of oral and sub-Tenon’s injections of corticosteroids produced no improvement. Examination here in June 1989 revealed visual acuity 20/20 right eye, 20/25 left eye, a 3+ left afferent pupillary defect, and marked constriction of the left visual field to counting fingers. In the left eye there were 1+ vitreous cells, mild blurring of the optic disc margin, some narrowing of the retinal vessels and diffuse hypopigmentation of the pigment epithelium in the mid- and peripheral fundus (Fig. 7). Fluorescein angiography showed evidence of these changes as well as mild diffuse intraretinal staining in the posterior fundus. The right eye was normal. Visual field examination was unchanged. Electroretinography revealed extinguished rod and markedly reduced cone function in the left eye. Responses in the right eye were normal. Her last examination in May 1992 revealed no change in her eye examination and electroretinographic findings. She still complained of photopsia.

**Case 10**

In July 1988, a 36-year-old woman developed allergic bronchitis and conjunctivitis that she attributed to cleaning a dusty attic. One month later she struck the right side of her head on her car door.
Several weeks later she became aware of loss of side vision, blurred central vision and "an orange spray of lights" temporally in the right eye. Her local ophthalmologist noted a peripheral round retinal hole, some narrowing of the peripheral retinal vessels, cystoid macular edema, and unexplained loss of the temporal visual field in the right eye. The left eye was normal. In retrospect, the patient recalled that defective temporal vision in the right eye was probably the cause of her head injury. The retinal hole was treated with photocoagulation, and she was referred for medical and neurological evaluations that were negative. Her medical history was positive for an episode of pseudomembranous colitis in 1985, severe gastroenteritis of undetermined cause in 1987, and recurrent episodes of herpetic gingivitis and dermatitis. Over the following few months there was progressive loss of the peripheral visual field and narrowing of the retinal vessels in the right eye. An electroretinogram in October 1988 revealed marked reduction of the A and B wave amplitudes in both photopic and scotopic conditions in the right eye. The left eye was normal. On examination here in December 1988, her visual acuity was 20/30 right eye and 20/15 left eye. In the right eye she had a 2+ afferent pupillary defect, 1+ vitreous cells, cystoid macular edema, narrowing of the retinal vessels, diffuse slight depigmentation of the retinal pigment epithelium, and marked constriction of the visual field (Fig. 8). The left eye was normal except for a small focal atrophic scar superior to the optic disc (Fig. 8). Fluorescein angiography revealed a large juxtapapillary zone of early hyperfluorescence and no evidence of late staining in the macular area of the right eye (Fig. 8). Frequent visual field examinations showed stabilization of the field loss in the right eye by March 1989 (Fig. 1). During this time the photopsia and the cystoid macular edema diminished. The patient remained...
asymptomatic in the left eye until September 1990, when, soon after developing allergic bronchitis and conjunctivitis, she experienced the rapid onset of photopsia and visual field loss in the left eye. It began in the temporal field and spread to involve much of the peripheral field within several weeks. Examination confirmed the visual field loss and revealed trace vitreous cells and a normal fundus of the left eye. One month later visual acuity was 20/25 bilaterally. In the left eye there was narrowing of the retinal vessels. Fluorescein angiography was unchanged in both eyes. Cancer-associated retinopathy was suspected. Medical evaluation including CT scans of the chest and abdomen, mammograms, serum protein electrophoresis, lupus anticoagulant, anticardiolipin, and antithrombin III were within normal limits. Serological titers for Lyme disease, Epstein-Barr virus, Coxsackie virus, herpes simplex virus IgM, herpes zoster IgM, and influenza A and B virus were negative. Herpes zoster virus IgG was positive 1:256. An assay for circulating antibodies to retinal antigens was negative.

Despite orally administered prednisone 60 mg/day for 2 months, the visual field loss progressed and she developed blurred vision and cystoid macular edema. Electroretinography revealed extinguished scotopic and minimal photopic responses in both eyes. Electrooculography revealed an Arden ratio 1.27 right eye and 1.14 left eye. Progression of the visual field loss in the left eye stopped after 4 months (Fig. 1). By December 1991, the fundoscopic and angiographic findings in the left eye were the same as the right eye (Fig. 8). On last examination, in June 1992, her visual acuity was 20/25 right eye and 20/20 left eye. There were 1+
vitreous cells and cystoid macular edema bilaterally. Visual fields were unchanged.

**Case 11**

In July 1991, a 41-year-old woman presented with the history that 2 years previously in Cuba she noted the onset of “firecrackerlike” lights and a scotoma that began temporally and rapidly spread to involve all of the peripheral field of the right eye. She was examined by several ophthalmologists who initially could find no cause for the visual loss. Neurological evaluation was unremarkable. Later diagnoses of posterior uveitis and unilateral retinitis pigmentosa were made. Unsuccessful treatments included oral corticosteroids, vitamin A, plasmapheresis, and “artery transplant” to the temporal wall of the right eye. An electroretinogram in June 1990 was reported as extinguished in the right eye and subnormal in the left eye. At the time of examination here she complained of chronic photopsia and visual loss in the right eye. Her visual acuity was 20/40 right eye, 20/20 left eye. In the right eye there was a 1+ afferent pupillary defect, 1+ vitreous cells, cystoid macular edema, diffuse depigmentation of the pigment epithelium, and narrowing of the retinal vessels. The left eye was normal except for mild pigment epithelial mottling anterior to the equator. Visual field examination showed marked concentric constriction of the field in the right eye and slight nasal constriction in the left eye (Fig. 4). An electroretinogram revealed extinguished rod function and markedly abnormal cone function in the right eye. Electroretinography was normal in the left eye. Four months later her visual field and other findings were unchanged.
FIG. 8. Case 10: (A & B): Right and left eyes, December 1988. Note narrowing of retinal blood vessels, juxtapapillary pigment epithelial depigmentation, cystoid macular edema (arrow) in the right eye, and a depigmented scar (arrowhead) in the left eye. (C): Angiogram showing juxtapapillary zone of depigmentation and no staining in the area of cystoid macular edema. Continued.
Case 12

In late 1987, a 34-year-old woman noted loss of peripheral vision nasally in the right eye associated with photopsia and light sensitivity. One year previously she had had a prolonged illness associated with infectious mononucleosis. Her past medical history was otherwise negative except for an allergic reaction to penicillin. On initial eye examination in August 1988, her visual acuity was 20/25 bilaterally, and the fundi were normal except for a few flecks of pigment temporally in the right eye and mild mottling of the pigment epithelium peripherally bilaterally. Visual field examination revealed an arcuate scotoma that involved most of the superior and nasal visual field of the right eye (Fig. 4). There was enlargement of the blind spot in the left eye. Fluorescein angiography, Farnsworth D-15 color panel and visual evoked potential were normal. Neurological examination that included electroencephalography was within normal limits. IgG and IgM titers for Epstein-Barr virus were positive. Electroretinography showed reduction of the B-wave to 70 microvolts with normal implicit times in the right eye; reduced rod and cone amplitudes in the right eye; reduced rod amplitudes and borderline cone amplitudes and timing in the left eye. In May 1990, she returned complaining of further visual loss in the right eye. Visual acuity was 20/50 right eye and 20/20 left eye. The visual field revealed new involvement of the superonasal paracentral field of the right eye. No other changes were present. Spinal fluid examination and serum Lyme titers were negative. Screening for HLA group A, B, C, DR, and DQ antigens was positive for A3, A31(19), B8, B35, Bw6, Cw4, Cw7, DR3, DR4, DQ2, DQ3, DR52, and DR53.

The patient received a 2-month course of oral prednisone 80 mg/day at tapering doses, supplemented with several sub-Tenon’s injections of prednisolone, followed by a 2-month course of oral acyclovir 800 mg five times daily. Between October 1990 and May 1991, visual field examinations revealed development of a small superior paracentral arcuate scotoma in the left eye. Repeat spinal fluid and serological examinations for Lyme disease were negative. Nevertheless, the patient received cephalothin intravenously for 13 days before it was discontinued because of diarrhea and fever. Orally administered vancomycin hydrochloride 100 mg-bid was given for 1 month. The patient noted no improvement, and the acuity in the right eye declined to 20/400 by November 1991. In May 1992 her visual acuity, visual field, and electroretinographic findings were unchanged.

Case 13

On June 15, 1990, a 17-year-old male student with a 3-week history of coryza and allergic rhinitis...
Case 14

In February 1982, a 23-year-old woman developed photopsia and paracentral scotomata that corresponded with multiple reddish-orange outer retinal lesions typical of acute macular neuroretinopathy in the left eye. The lesions and the photopsia gradually disappeared, but some of the paracentral scotomas remained until January 1987, when she noted the acute onset of photopsia, multiple small central scotomas, and a large temporal scotoma in the left eye. She described the photopsia as “multiple dancing spots of light, like bacteria under a microscope” within each of the scotomatus areas. Her visual acuity in the left eye was 20/80. The fundus of the left eye showed multiple grey-white lesions scattered in the peripheral macular and juxtapapillary areas and fluorescein angiographic changes typical for the multiple evanescent white-dot syndrome. There were multiple rings of early pinpoint hyperfluorescence and patchy areas of late staining in the macular and juxtapapillary regions. There was also staining of the optic disc. Amsler grid testing showed multiple small scotomas involving the nasal half of the grid and a large scotoma affecting most of the temporal half of the grid. Electroretinography revealed moderately reduced rod and cone responses in the left eye. The white spots disappeared within several weeks, the visual acuity returned to 20/20 within 2 months. She continued to be bothered by the temporal scotoma and the photopsia, particularly in bright light. By July 1987, there was evidence of slight depigmentation of the pigment epithelium in the juxtapapillary area as well as the temporal periphery in the left eye. A repeat electroretinogram in August 1988 was unchanged. In June 1992, she was still aware of the temporal scotoma and photopsia in the left eye. Her eye findings were unchanged. Goldmann field examination revealed a 20-degree scotoma involving the blind spot of the left eye. Fluorescein angiography revealed a prominent juxtapapillary zone of pigment epithelium depigmentation in the left eye that was not evident in her previous angiogram in January 1987.

Case 15

A 48-year-old woman complained of floaters and flashes of light inferiorly in the left eye of 3 months duration. Visual acuity was 20/25 right eye and 20/30 left eye. In the left eye there were 2+ vitreous cells and the left optic disc margins were indistinct. In both eyes there were many widely scattered fo-
cal atrophic chorioretinal scars that were most prominent in the superior temporal quadrants in the midperiphery. There was no evidence of chorioidal neovascularization. The diagnosis was the pseudo-presumed ocular histoplasmosis syndrome. One year later she returned, complaining of recent acute loss of vision, a temporal scotoma, photopsia, and light sensitivity in the left eye. Her visual acuity was 20/20 right eye and 20/80 left eye. There was a 2+ left afferent pupillary reaction. The fundi were unchanged except for slight narrowing of the retinal arteries in the left eye (Fig. 9). She missed all but one of the pseudoisochromatic plates with the left eye. There was marked enlargement of the blind spot and loss of a large segment of the inferior nasal field in the left eye. The diagnosis was retrobulbar neuritis. Laboratory studies, including chest radiograph, FTA-ABS, RPR, and tuberculin and mumps skin tests were normal. Lyme disease index was 1.3 (normal <1) and Lyme disease IgG titer was 1:128 (presumptive evidence of recent infection). Epstein-Barr viral titers were capsid antigen (IGG) 1:40, and nuclear antigen 1:40 (normal 1:10). Angiotensin-converting enzyme level was 15. Electroretinography revealed markedly reduced rod and mixed rod-cone amplitudes and extinguished cone responses in the left eye. The responses in the right eye were normal. Nine months later the eye findings were unchanged.

FINDINGS

Cases 1–13

Tables 1 and 2 summarize the demographics and the eye findings in these patients at the time of their presentation to the referring physician. Table 3 summarizes their eye findings at the time of my initial examination that occurred between 2.5 weeks and 24 months (mean and median: 5

FIG. 9. Case 15: Left eye. Top & Bottom: Note vitreous haze, blurred optic disc margins, narrowing of retinal arteries, and focal areas of depigmentation in the periphery.
months) after the onset of their symptoms. Table 4 summarizes their eye findings at their final examination that occurred between 6 and 71 months (mean: 33 months; median: 27 months).

These predominantly young female (77%) patients experienced rapid onset of visual field loss that most frequently involved the superior and temporal quadrants, often included the blind spot, and only occasionally caused loss of visual acuity. During the early course of the disease, 18 of 22 affected eyes (82%) had 20/30 or better visual acuity. The scotomas typically increased in size within a matter of days or weeks before stabilizing. In some cases enlargement continued for 2 to 6 months. Several patients complained of progression beyond 6 months, but this could not be documented objectively. In most cases the visual field loss in the two eyes was asymmetric. In all but four patients, depigmentation of the retinal pigment epithelium corresponding with part or all of the zones of visual loss occurred usually within several months (Figs. 2, 3, 5–8). Initially, this change was subtle ophthalmoscopically but was easily detected with fluorescein angiography that demonstrated prompt perfusion of the underlying choriocapillaris. Narrowing of the retinal vessels occurred in the zones of depigmentation, particularly when they were large and involved the peripheral retina. Fluorescein angiography in such cases showed evidence of increased retinal circulation.

<table>
<thead>
<tr>
<th>TABLE 1. Patient characteristics (N = 13)</th>
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<tbody>
<tr>
<td>Characteristic</td>
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<td>Age at presentation</td>
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<th>TABLE 2. Characteristics of eyes at presentation to referring physician (N = 22)</th>
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<td>Characteristic</td>
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<td>Visual acuity</td>
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<td>Light eye affected</td>
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<td>Scotoma</td>
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<td>Photopsia</td>
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<td>Subjective floaters</td>
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<td>Normal fundus</td>
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<th>TABLE 3. Characteristics of eyes at initial examination by the author (J.D.M.G.) (N = 22)</th>
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<td>Characteristic</td>
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<tr>
<td>Visual acuity</td>
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<tr>
<td>Vitreous cells</td>
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<td>Normal fundus</td>
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<tr>
<td>Zonal atrophy of retinal pigment epithelium</td>
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<tr>
<td>Color vision abnormal</td>
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<td>Electroretinogram abnormal</td>
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<tr>
<td>Electrooculogram abnormal</td>
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<td>Visual evoked response abnormal</td>
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* Data not always available on all 22 eyes.

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<th>TABLE 4. Characteristics of eyes at most recent examination (N = 22)</th>
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<td>Normal fundus</td>
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Vitreous cells were observed in either one or both of the affected eyes of 11 patients. In 3 with bilateral involvement, cells were present only in the eye with more widespread visual field loss. The vitreous cells were graded as trace to 1+ in 12 eyes and 2+ in 3 eyes. Patients with 2+ cells had large field defects and 2 of them were examined within the first week after onset of symptoms.

Two patients developed focal retinal perivenous infiltration or sheathing in the affected eyes (Fig. 2). Mild optic disc swelling was suspected in one patient but failed to change in its appearance several years later. Fluorescein angiography demonstrated some retinal and optic disc vascular leakage in 4 eyes (3 patients), including one with mild cystoid macular edema (Fig. 6). In one patient with bilateral cystoid macular edema, angiography failed to show staining (Fig. 8). Fluorescein angiography was done during the first few weeks after the onset of symptoms in only 5 patients, and was within normal limits in all of them.

While all patients had electroretinography, it was done in only 2 patients during the first month of their illness. Most of the affected eyes showed only mild to moderate reduction in rod and cone amplitudes. In a few eyes, the responses were within the lower range of normal but were lower than in the unaffected eye. Even in the most severely affected eyes, the ERG was extinguished in only one patient who later showed ERG evidence of some cone function. In the lesser affected eyes the cone responses generally were affected more than rod responses, whereas the reverse was true in the eyes with severe peripheral field loss.

Six patients had evidence of bilateral involvement at the time of presentation. Two of these were asymptomatic in one eye. Three patients had delayed involvement of the fellow eye. In two patients it occurred after an interval of 2 years. In one patient the time of fellow eye involvement that was unassociated with symptoms was unknown. One patient (Case 12) developed a small segmental enlargement of a scotoma in both eyes at 22 and 34 months after the onset of symptoms. This was associated with loss of visual acuity in one eye.

Cases 14 and 15 shared several features demonstrated in cases 1–13. The shared features included acute loss of zones of visual field (including blind-spot enlargement); absence of fundus findings to explain the field loss; and electroretinographic evidence of outer retinal damage. In Case 14, these features were accompanied by fundus lesions typical of the multiple evanescent white-dot syndrome that occurred 5 years after acute macular neuropathy in the same eye (1). In Case 15 they occurred in one eye of a patient with evidence of the pseudo-presumed ocular histoplasmosis syndrome in both eyes.

**DISCUSSION**

Acute zonal occult outer retinopathy seems an appropriate descriptive name for the syndrome demonstrated by Cases 1–13. All these cases shared the following features: rapid loss of one or more large zones of outer retinal function, minimal fundus changes, electroretinographic abnormalities, and permanent visual field loss that, in most cases, was associated with delayed development of visible atrophic changes in the pigment epithelium and narrowing of the retinal vessels. Both clinical and electrophysiological findings suggest that the retinal photoreceptors and pigment epithelium are the primary loci of disease in this syndrome. Acute dysfunction of these cells is usually accompanied by normal fundus and fluorescein angiographic findings. This dysfunction may be temporary or permanent. When permanent, it is usually associated with the late development of depigmentation of the pigment epithelium in the affected zones in the absence of angiographic evidence of alteration in perfusion of the choriocapillaris. When these zones are large, there may be noticeable narrowing of the retinal vessels, angiographic evidence of increased retinal circulation time, and eventually migration of pigment into the overlying retina in a bone-spicule pattern. These findings suggest severe damage to, and loss of, the receptor cells within these zones of pigment epithelial depigmentation. In some patients the zone of prolonged visual field loss may be associated with no fundoscopic or angiographic abnormalities. This implies that in these zones the dysfunctional receptor cells may still be viable and that restoration of function is still possible.

There is little evidence that the retinal ganglion cells are affected by this disease. Evidence that suggests the outer retina is primarily affected includes the configuration and density of the visual field defects, the localization of photopsia to the zones of field loss, the accentuation of both in bright light, the electroretinographic abnormalities, the frequent development of zones of pigment epithelial atrophy corresponding with the visual fields loss, and the failure of development of optic atrophy, even in patients with large permanent field defects affecting the macula.

The cause of acute outer retinal dysfunction in these patients is unknown. The preservation of retinal transparency and normal color of the pig-
abnormalities will avoid unnecessary neurological investigations. In some patients, electroretinogram (ERG) amplitudes may be borderline normal, and a focal ERG may be required to detect the abnormality (14). In both instances these minimal ERG findings should be interpreted with caution before excluding other causes for the visual field loss.

Only 1 of 6 patients who received orally administered corticosteroids that in 2 cases was supplemented with sub-Tenon's injection of cortisone showed improvement. Two patients were treated with oral acyclovir. One received it 2 weeks after onset of severe field loss in his fellow eye and had no further progression during 1 month of follow-up. The other received it 2 months after development of a new scotoma that failed to respond to a course of systemic corticosteroid treatment. Although the visual field stabilized, the acuity declined. Because of slight enlargement of her scotoma in the lesser involved fellow eye, 8 months later this same patient received ceftriazone sodium and vancomycin hydrochloride because of suspected Lyme disease. The visual fields were unchanged 1 year later.

The visual prognosis for most patients appears to be good. However, longer follow-up is necessary to determine the natural course of this disease. All of the patients reported in this series have retained 20/25 or better visual acuity in at least one eye. One patient is legally blind because of severe loss of peripheral visual field.

I believe that Cases 1 through 13 have the same disorder, and that they represent only part of the spectrum of what probably is either one disease or closely related diseases that have been described previously as the multiple evanescent white-dot syndrome, acute idiopathic blind-spot-enlargement syndrome, acute macular neuroretinopathy, and multifocal choriotretinitis resembling the presumed ocular histoplasmosis syndrome. In 1984 Jampol and colleagues (12) described the multiple evanescent white-dot syndrome (MEWDS) in 10 young women and 1 man with unilateral acute visual loss, multiple rapidly fading white outer retinal lesions, electroretinographic abnormalities, and spontaneous recovery of vision and electrophysiological function within several months. Other findings included vitritis, punctate white or orange foveal flecks, and in approximately 50% of patients, a history of an antecedent viral-like infection. Takeda and colleagues (13) independently reported the same disease in 4 young adults. There was minimal evidence of response to treatment in these patients.

In 1988 Fletcher and colleagues (14) reported the acute idiopathic blind-spot-enlargement syndrome...
(AIBSES) in predominantly young women with acute unilateral loss of vision, photopsia, dense scotomas centered around the blind spot, normal fundus, and abnormal electoretinographic findings. Hamed and colleagues (15), Aaberg (16), and Gass and Hamed (1) presented evidence that MEWDS and AIBSES are the same disease. In 1990, Gass and Hamed (1), and more recently Singh and colleagues (17) reported evidence that some patients with MEWDS and AIBSES develop paracentral, reddish-orange outer retinal lesions characteristic of acute macular neuroretinopathy (AMN), a syndrome originally described in 1975 by Bos and Deutman (18). At the January 1991 Macular Society Meeting I presented evidence for the following:

1. Of patients seen at the Bascom Palmer Eye Institute with MEWDS and AIBSES, 25% either had, at the time of presentation or subsequently developed, either one or both, multifocal active and atrophic fundus lesions typical for that seen in patients with the presumed ocular histoplasmosis syndrome (P-POHS) (19-21).

2. Patients with AIBSES may present with large zones of peripheral visual field loss, not necessarily continuous with the blind spot, and later develop fundus changes that simulate retinitis pigmentosa and cancer-associated retinopathy.

3. MEWDS, AIBSES, AMN, and P-POHS may have a common cause.

Singh and colleagues (17) and Khorram and colleagues (22) recently described acute enlargement of the blind spot in patients with the presumed ocular histoplasmosis syndrome (P-POHS) and with multifocal choroiditis. Singh and colleagues (17) suggested that POHS is but one of multiple causes of acute blind spot enlargement. Callanan and Gass (23), on the other hand, have recently presented further evidence that MEWDS, AIBSES, and P-POHS may have a common cause.

Cases 1-13 share the following features in common with MEWDS, AIBSES, AMN, and P-POHS: acute visual loss in predominantly young women, acute blind-spot enlargement in the absence of fundus changes to explain it, electoretinographic abnormalities, retention of good visual acuity in most cases, and all of these syndromes have been reported since 1975.

The literature contains limited information concerning the frequency of blind-spot enlargement in patients with P-POHS and AMN. Results of visual field examination are often not included in reports of these disorders. Of interest in this regard is that the two initial reports of 15 patients with MEWDS described blind-spot enlargement in only 2 patients and photopsia in none, yet both occur in most of these patients (1). Dreyer and Gass (19) in their report of 28 predominantly female patients with P-POHS did not describe visual field findings, yet they did report electoretinographic abnormalities in 11 of 16 patients tested, and in 8 it showed moderately severe to extinguished electoretinographic responses in one or both eyes. Some of these patients probably had enlarged blind spots as well as other large zones of visual field loss similar to Cases 1 to 13 and Case 15.

The acute focal lesions of P-POHS may be difficult to distinguish from those of MEWDS. While those of P-POHS are generally more intensely white, sharply circumscribed, often clustered in the macular area, more homogeneously stained with fluorescein, and more likely to cause a focal area of depigmentation of the pigment epithelium similar to POHS, some are indistinguishable in all respects from those of MEWDS. Although the lesions of P-POHS are more likely to be complicated by subretinal neovascularization, those of MEWDS are not immune to this complication (23,24). The lesions of both are located at the retina-choroid interface. The primary difference between the two may be the intensity of the patients immune response to the same insult. The location of active lesions in MEWDS and P-POHS may be partly or completely outside of the zone of dense visual field loss that in MEWDS often includes the blind spot. It is curious that, while the reaction responsible for the focal white lesions and that causing the zonal loss of vision both appear to occur at the same level, one results in a visible change and the other does not.

Only 9 patients with AMN have been seen at the Bascom Palmer Eye Institute since the first one presented in 1972. Of these, 2 (including Case 14) have had evidence of both MEWDS and acute blind spot enlargement (1). None of the other 7 patients had a visual field examination other than Amsler grid testing, which showed sharply defined scotomas that precisely correlated with the reddish lesions at the level of the outer retina. The biomicroscopic features of these often subtle lesions, their precise correlation with the scotomas, the absence of fluorescein angiographic evidence of pigment epithelial cell damage, and their frequent association with electoretinographic abnormalities, suggest that they involve primarily the retinal receptor cells and that the retina is affected beyond the confines of the reddish lesions that are never found outside the macular area. Sieving and colleagues have demonstrated reduction of early retinal receptor potential in AMN (25). Future visual field investigations of patients with AMN and
P-POHS probably will demonstrate the frequent presence of occult zones of outer retinal damage.

Acute loss of large zones of outer retinal function in the absence of fundus changes occurring predominantly in women is the common denominator that links Cases 1 to 13 with patients with MEWDS, AIBSES, AMN, and P-POHS. The female predilection suggests the possible role of autoimmunity in the pathogenesis of these disorders. Rather than designating a separate name for these 13 patients, I propose that acute zonal occult outer retinopathy is an appropriate and inclusive name for this group of disorders that may prove to have the same, or closely related, underlying causes (Table 5).

### REFERENCES

Visual Recovery from Radiation-Induced Optic Neuropathy
The Role of Hyperbaric Oxygen Therapy

F.-X. Borruat, M.D., N. J. Schatz, M.D., J. S. Glaser, M.D., L. G. Feun, M.D., and L. Matos, M.D.

Optic neuropathy resulting in permanent visual loss is an infrequent delayed complication of radiation therapy. Hyperbaric oxygen therapy (HBO) has been used to treat such a complication, but its efficacy is controversial. We report a patient who presented with radiation-induced optic neuropathy 17 months after irradiation for a left maxillary antrum melanoma. HBO fully reversed visual loss in the more recently involved eye, and slightly improved vision in the earlier affected eye.

Key Words: Hyperbaric oxygen—Radiation necrosis—Optic neuropathy.

CASE REPORT

A 45-year-old woman presented in May 1990, with recent onset of left nasal obstruction and bleeding. A melanoma of the left maxillary sinus invading the nasal cavity was found and extensive sinus surgery was performed. Despite postoperative 8-mm inferior displacement of the left orbital contents, visual acuity remained at 20/20 and visual fields were full in both eyes. Between July 5 and August 7 of 1990, 5,000 rads were delivered to the left maxillary sinus (20 sessions of 250 rads over 33 days), and 4,250 rads to the left neck (17 sessions of 250 rads over 27 days), without overlap of radiation fields. On October 15, 1990, chemotherapy was commenced with intravenous dacarbazine and oral piritrexim, an experimental folate antagonist (7). Dacarbazine had to be discontinued on August 1991, due to intolerable fatiguability following infusion and the patient remained on only oral piritrexim for the next 7 months. She remained in partial remission and visual function was unchanged in both eyes.

Early February 1992, 21 months after surgery and 17 months after completion of irradiation, the delayed necrosis of the intracranial optic nerves or chiasm is a recognized complication of ionizing radiation, characterized by abrupt and permanent visual loss affecting one or both eyes (1-3). Intervals from irradiation to symptom onset vary from less than 6 months to 3 years. Treatment of radiation optic neuropathy (RON) with hyperbaric oxygen (HBO) has been shown to stop or reverse the visual loss (4), but its efficacy has been challenged (5,6). We here report the benefits of HBO in a patient who presented with visual loss, occurring 17 months after radiotherapy.
patient noted left visual loss. On February 10, 1992, visual acuity was 20/20 OD and 20/70 OS with a left pupillary afferent defect. Goldmann visual field revealed an arcuate nasal inferior defect in the left eye (Fig. 1, top). The right optic disk was normal and the left showed temporal pallor. No retinal lesions were seen. Magnetic resonance imaging (MRI) was recommended but not carried out.

At 15 days later, the patient returned with further visual loss: left vision now “no light perception” (NLP), right acuity still 20/20, but with temporal hemianopia on Humphrey visual field (Fig. 1, middle). MRI performed the same day revealed an enlarged left intracranial optic nerve and left hemichiasm, which enhanced after gadolinium injection (Fig. 2). No recurrence of the tumor was detected either clinically or by MRI. The patient underwent HBO (three periods of 30 minutes of 100% oxygen at 2.4 atm, separated by 2 periods of 10 minutes of normal air breathing twice a day for 2 days, then 5 to 6 times/week, 35 sessions in to-

![FIG. 1. Visual fields. Top: Goldmann perimetry: normal visual field in the right eye; the left eye shows an arcuate nasal inferior loss. Middle: Left vision is no light perception. Automated static threshold perimetry (Humphrey, 30-2) reveals a dense temporal hemianopia of the right eye. Bottom: Left vision is light perception. Automated static threshold perimetry (Humphrey, 30-2) shows a remarkable recovery of the temporal hemianopia.](image)
tal). The patient also received intravenous methylprednisolone 500 mg q6h for 5 days, followed by oral prednisone, 60 mg daily, tapering over 8 weeks.

At 13 days after therapy was initiated, marked resolution of the right temporal hemianopia was noted, further improving 2 weeks later (Fig. 1, bottom). Three weeks after completion of HBO therapy, vision was 20/20 OD and light perception OS; the right visual field (Humphrey, 30-2) was normal. MRI was repeated and showed decreased swelling of the left intracranial optic nerve and chiasm with only slight enhancement after gadolinium injection.

**DISCUSSION**

Delayed necrosis of the optic nerves and chiasm is a well-recognized complication of radiotherapy. Irradiation causes tissue ischemia secondary to a progressive obliterative endarteritis of the microvasculature. Pathology studies demonstrate myointimal and endothelial proliferation of small arteries and narrowing of the vessel lumen with fibrinoid necrosis (8). Skin biopsies from irradiated areas showed the presence of hypocellular and hypovascular tissue that is unable to regenerate supportive vessels and transcutaneous oxygen measurement in irradiated areas revealed tissue oxygen tension at 30% of nonirradiated areas (9). Despite the presence of an endarteritis, the role of high-dose steroids is uncertain as no cases of RON has been reported to improve with steroids only.

RON has been reported to occur as early as 2 months and as late as 7 years after completion of radiotherapy (Fig. 3). However, 90% of RON cases occur within 3 years of irradiation with a mean onset at 12 months (2,3,5,10). In the present case,
visual loss began suddenly 17 months after completion of irradiation. A left retrobulbar optic neuropathy evolved rapidly, progressing to no light perception. Two weeks later, evidence of chiasmal involvement occurred with a dense temporal hemianopia, but preserved visual acuity in the right eye. MRI revealed enlarged left intracranial optic nerve and swollen left chiasm, both enhanced with gadolinium (Fig. 2). These MRI characteristics have been previously demonstrated in RON (10). No other cerebral involvement was detected on MRI and no local recurrence of the sinus melanoma was evident.

HBO therapy produces a steep oxygen gradient between irradiated and non-irradiated tissues. Such an oxygen gradient directly enhances fibroblastic activity, collagen synthesis, and neovascularization in the irradiated tissues (9). HBO is presently the only available treatment capable of creating an environment that allows the reversal of radiation-induced tissue damage. From 20 to 30 sessions of 100% oxygen breathing at 2.4 atm for 90 min each day has been successfully used for problem wounds in oral and maxillofacial surgery following irradiation (9). Since angiogenesis is a progressive event with an initial lag phase, we suggest the use of twice-daily treatments during the first week if vision is deteriorating.

Guy and Schatz (4) first reported visual improvement in RON when treated early with HBO after onset of visual loss, within 2 days if possible. The effectiveness of HBO in RON was challenged by Roden and coworkers (5), but in that report all patients were treated 2 to 12 weeks following visual loss and breathing oxygen at only 2.0 atm.

Our patient was treated 15 days after the onset of left visual loss and 2 days after the loss of the right temporal visual field. There was full recovery of the right hemifield and the left vision slightly improved to light perception. The role of early therapy of RON is emphasized; the key element is the commencement of HBO therapy as soon as vision starts to deteriorate. The dramatic visual recovery in our case emphasized both the benefits of hyperbaric oxygen therapy and the need for starting therapy soon after visual loss, within 2 days, if possible.

REFERENCES


FIG. 3. Latency for the development of radiation-induced optic neuropathy: the cumulative data for 50 patients with radionecrosis of optic nerve and/or chiasm are plotted on this histogram (2, 3, 5, 10, and present case). Median latency is 12 months; 90% of cases presented within 3 years of radiation.
Metastatic Lesion of the Optic Nerve

A. M. Mansour, M.D., Kevin Dinowitz, M.D., Gregory Chaljub, M.D., and Faustino C. Guinto, M.D.

Metastatic disease to the optic nerve is uncommon (1-8). Optic nerve involvement has been described as an extension from choroidal, retinal, orbital, or central nervous system metastatic foci. Isolated optic nerve metastatic disease is extremely rare. We present the case of an isolated circumscribed metastatic lesion to the retrobulbar portion of the optic nerve detected radiographically.

Key Words: Metastatic disease—Optic nerve—Radiography.

CASE REPORT

A 41-year-old woman presented with a 2-week history of progressive visual loss in the left eye. She underwent a left simple mastectomy in 1985 and a modified radical right mastectomy in 1989 with postoperative radiotherapy and chemotherapy for bilateral primary infiltrating ductal adenocarcinoma. Metastatic brain disease was diagnosed in February 1992 and was controlled by surgical resection of a left frontal mass and by radiation therapy to the whole brain (3,000 cGy dosage in 10 sessions ending in March 1992). Upon presentation in early September 1992, ophthalmic evaluation of the left eye revealed a visual acuity of hand motion, marked afferent pupillary defect, and mild disc pallor. The right eye had mild background diabetic retinopathy and normal Goldmann visual fields. Computed tomography of the optic nerves revealed mild fusiform enlargement of the left optic nerve adjacent to the optic canal (Fig. 1). The differential diagnosis included carcinomatous leptomeningitis and infectious neuritis. Cerebrospinal fluid was negative for malignant cells. Cerebrospinal fluid cultures (including fungal and mycobacterial) were negative. Visual acuity of the left eye dropped to light perception 3 days later. Magnetic resonance imaging then revealed an enhancing 3- to 4-mm intraparenchymal lesion of the left optic nerve just before the optic chiasm, on gadolinium enhanced T1-weighted images (Figs. 2-5). Multiple 1-cm metastatic lesions were present in the parietal and the temporal lobes. The visual acuity did not improve following prompt initiation of radiotherapy (total dose of 1,400 cGy in 7 sessions). The visual status was unchanged after 1 month of follow-up. New metastases were found in the right parietal lobe and the femur in November 1992.

DISCUSSION

This is the first radiographic report of an isolated optic nerve metastatic lesion without retinal, choroidal, or optic nerve head involvement. The lesion was suspected by CT scan and was well delineated by magnetic resonance imaging. Due to its multiplanar capabilities, excellent soft tissue contrast, and no-beam hardening artifact from adjacent bone, magnetic resonance imaging is the imaging modality of choice over CT in prechiasmatic optic nerve pathology. Reports of retrobulbar optic nerve metastases (3,5,7-10) have usually dealt with involvement of the optic nerve sheaths. Intraparenchymal metastasis as in the present case (focal lesion, normal cerebrospinal fluid, normal cranial nerves besides the left optic nerve) needs to be differentiated from the more common meningeal carcinomatosis (or carcinomatous optic neuropathy (10). In meningeal carcinomatosis, the cerebrospinal fluid is positive for malignant cells, and the patient often demonstrates signs of low-grade meningitis, as well as signs of damage to one or several cranial nerves. There is usually diffuse tumor infiltration of the leptomeninges around the optic nerves resulting in compression and second-
ary compromise of blood supply leading to visual loss. Metastatic optic nerve disease manifested ophthalmoscopically in the majority of reported cases as a visible mass occupying the optic nerve head (3). Metastatic retrobulbar optic nerve disease may manifest as a retrobulbar neuritis (3,9). Visual loss can be progressive as the metastatic focus enlarges or can be sudden from complications such as central retinal vein occlusion (3). Most primary sites arise from the breast or the lung. Radiation therapy and chemotherapy may preserve vision if the intervention is performed early in the course of the disease. Other differential diagnoses in the present case include radiation neuritis (11,12). Radiation neuritis usually occur in patients with

FIG. 1. Axial postcontrast CT shows thickened optic nerve adjacent to the optic canal.

FIG. 2. Parasagittal T1-weighted magnetic resonance image without contrast shows prechiasmatic enlargement of the optic nerve (arrow).

FIG. 3. Parasagittal T1-weighted magnetic resonance imaging with gadolinium showing an enhancing 3-4 mm lesion (arrow) of the optic nerve before the optic chiasm.

FIG. 4. Coronal post-gadolinium T1-weighted image shows an enlarged left prechiasmatic optic nerve (arrow) with intraparenchymal enhancement. The right optic nerve (hollow arrow) is normal in size.
higher radiation doses (above 5,000 cGy), with radiation focused around the periorbital region (as in pituitary fossa tumors), and with a longer interval time between the radiation and the neuropathy (6 months interval in the present case). Infectious neuritis [bacterial, sarcoid (13), tuberculous (14), toxoplastic (15), and syphilitic (16)] is added to the differential diagnosis.

REFERENCES

A 16-year-old girl developed headaches and bilateral papilledema while taking minocycline for acne. The initial neuro-ophtalmologic evaluation was normal except for enlarged blind spots OU. An MRI scan demonstrated subtle abnormalities. A lumbar puncture was entirely normal except for an increased opening pressure. A tentative diagnosis of pseudotumor cerebri was made and the patient was treated with Diamox. A second MRI was unchanged, and a lumbar puncture performed while the patient was taking Diamox was entirely normal. The patient subsequently lost vision in both eyes, and a third MRI now revealed a supracellar enhancing mass. Biopsy and subtotal resection of the mass showed it to be a glioblastoma multiforme. This case emphasizes pitfalls in the diagnosis of pseudotumor cerebri. Careful follow-up and a high index of suspicion in pseudotumor cerebri syndromes are essential.

Key Words: Pseudotumor cerebri—Glioblastoma multiforme—Papilledema—Cerebrospinal fluid cytology—Cerebrospinal fluid protein—Minocycline.

Pseudotumor cerebri (PTC) is a condition characterized by elevated intracranial pressure, normal cerebrospinal fluid composition, and normal neuroimaging studies (1). Additionally, most patients have papilledema. Although PTC is often idiopathic, certain drugs, such as tetracycline and its analogs, can be associated with this condition (2-7). We report a case of glioblastoma multiforme that initially mimicked minocycline-induced pseudotumor cerebri.

CASE PRESENTATION

A 16-year-old girl presented to her pediatrician with complaints of daily, right-sided headaches of 12-months' duration associated with a 5-week history of intermittent, horizontal, binocular diplopia. Although sinus radiographs reportedly were consistent with sinusitis, a course of amoxicillin only transiently improved her symptoms, and she sought the opinion of an ophthalmologist. She was referred for neuro-ophtalmologic consultation after the general ophthalmologic examination revealed bilateral optic disc swelling.

The patient's past medical history was significant for acne treated with the tetracycline analog, minocycline, and a topical vitamin A preparation (Retin-A). She also had suffered from seasonal allergies treated with the antihistamine agents astemizole (Hismanal) and terfenadine (Seldane).

Neuro-ophtalmologic examination revealed best corrected visual acuity of 20/15 OD and 20/20 OS. Near vision was J-1 OU. Color vision utilizing Hardy-Rand-Rittler (HRR) pseudoisochromatic plates was 9.5/10 OD and 10/10 OS. Kinetic perimetry was normal; however, static perimetry revealed enlarged blind spots OU and a slight reduc-
tion in the mean deviation OD (Fig. 1). Pupils were normal without a relative afferent defect. A small esophoria of approximately 4 prism diopters was noted at distance and near. Corneal and facial sensation were normal bilaterally. Slit-lamp biomicroscopy was unremarkable OU. Ophthalmoscopy revealed bilateral, hyperemic swollen discs, right greater than left (Fig. 2). No spontaneous venous pulsations were observed in either eye.

An MRI was performed, which some neuroradiologists considered normal; however, others thought that there was subtle nonenhancing diffuse enlargement of both thalami, the optic chiasm, and the infundibulum (Fig. 3). A lumbar puncture revealed acellular cerebrospinal fluid (CSF) with an opening pressure of 340 mm of water. The protein concentration was less than 10 mg%, and the glucose was normal. Cytopathologic examination of the CSF revealed no malignant cells.

The patient was placed on acetazolamide (Diamox) 250 mg q.i.d. and she stopped using both minocycline and Retin-A. Her headaches improved, but 2 weeks after beginning therapy, she developed paresthesias. Accordingly, the Diamox was decreased to 250 mg t.i.d.

Repeat neuro-ophthalmologic examination and cerebral MRI 5 weeks later, were unchanged. A second lumbar puncture now revealed acellular CSF with an opening pressure of 185 mm of water, a protein concentration of 29 mg%, and normal glucose. CSF cytopathologic examination was again negative for tumor cells.

At 8 weeks after the initial presentation, the patient returned with complaints of visual loss OS. Additionally, she related a several-month history of amenorrhea. Examination now revealed best corrected visual acuity of 20/25-2 OD and 20/80 OS. Color vision was 10/10 OD and 9/10 OS, but there was a mild left relative afferent pupillary defect, and static perimetry demonstrated bitemporal hemianopic visual field defects (Fig. 4). The papilledema was unchanged.

The patient was admitted to the hospital and a third MRI with gadolinium (Gd-DTPA) was performed. This revealed a large supracellar mass with diffuse involvement of the diencephalon and optic chiasm. The mass showed irregular enhancement following administration of Gd-DTPA (Fig. 5). The patient was placed on dexamethasone and scheduled for surgery. While awaiting surgery, she experienced an episode of bradycardia and hypotension accompanied by worsening headache. An emergency computed tomographic (CT) scan revealed subarachnoid and intraventricular blood caused by hemorrhage within the tumor.

An emergency right pterional craniotomy was performed, and the tumor was partially resected. Histopathologic examination revealed abnormal cells with prominent nuclei, vascular endothelial proliferation, pseudopalisading, and areas of necrosis characteristic of glioblastoma multiforme (Fig. 6). The glial fibrillary astrocytic protein (GFAP) stain was positive (Fig. 7).

The patient developed hydrocephalus in the postoperative period and underwent placement of a ventriculoperitoneal shunt. She was subsequently treated with chemotherapy consisting of

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**FIG. 1.** Static perimetry (24-2 strategy) at presentation shows enlarged blind spots OD and OS.
FIG. 2. Bilateral optic disc swelling worse in the right eye.

carmustine (BCNU) and cisplatin and with hyperfractionated radiation therapy. Despite treatment, a follow-up MRI 2 months after surgery demonstrated tumor extension into the corpus callosum and both frontal lobes with edema and mass effect.

DISCUSSION

This case, in which a glioblastoma multiforme simulated pseudotumor cerebri (PTC), is noteworthy from several standpoints. First, the patient was a 16-year-old girl. PTC typically occurs in young women; however, the peak incidence of glioblastoma multiforme occurs between the fourth and sixth decades with a male predominance (1). In one study of patients with glioblastoma, less than 3% of patients were children (8).

The second aspect concerns the presence of increased intracranial pressure. When associated with glioblastoma multiforme, the intracranial hypertension can be caused by several mechanisms, including the tumor's critical mass, obstruction of
the intracranial venous outflow and blockage of the CSF pathways (9). Frankel and German (10) reviewed the results of 122 lumbar punctures in 219 cases of glioblastoma multiforme and found that 80% had increased intracranial pressure. In our patient, the diagnosis of PTC was supported by the finding of a normal CSF pressure at the time of the second lumbar puncture.

The third aspect of this unusual case was the normal CSF protein concentration. The concentration of protein in the CSF in patients with PTC is, by definition, normal. It may even be low, suggesting an increased rate of CSF absorption in patients with this syndrome (9). In contrast, CSF analyses in glioblastoma multiforme typically reveal an increased CSF protein level (11). Merritt and Fremont-Smith (12) found that 68% of patients with hemispheric glioma had CSF protein content greater than 45 mg/dL. Similarly, Frankel and German (10) found that CSF protein content was increased in 76% of patients with glioblastoma multiforme. The increase in CSF protein concentration with CNS tumor correlates with disruption of the blood-brain barrier caused by changes in endothelial cell permeability (9). In patients with suspected neoplasm, when neuroimaging is negative, the increased CSF protein content is an early and sensitive indicator of increased endothelial cell permeability.

FIG. 3. A: Axial T2-weighted image showing apparent enlargement of both thalami, left greater than right. No abnormal high signals are noted. B: Coronal T1-weighted image shows apparent enlargement of thalami and a diffusely enlarged optic chiasm and infundibulum. C: Coronal T1-weighted image with Gd-DTPA of same region as in B shows no evidence of enhancement.
ability associated with CNS neoplasms and absolutely eliminates the diagnosis of PTC (9). Nevertheless, the findings of Merritt and Fremont-Smith (12), Frankel and German (10), and others (9) indicate that about 20 to 30% of patients with glioblastoma multiforme have a normal CSF protein concentration.

The fourth aspect is related to the patient's acellular CSF noted on two different occasions. The CSF in patients with glioblastoma multiforme often shows a mild pleocytosis of 10 to 100 cells (1,9). Frankel and German found that 46% of the lumbar punctures in glioblastoma multiforme showed abnormal cell counts (10). In addition, the CSF cytopathologic examination in patients with glioblastoma multiforme often demonstrates malignant cells (9,11). In previous reports, the incidence of positive CSF cytopathology in cases of glioblastoma multiforme has ranged from 17% to 37.2% (13–18). Nevertheless, Bischoff (13) reported a false negative rate of CSF cytopathology in 9 of 20 (45%) cases of glioblastoma multiforme. This high var-
ability among the different series may reflect the differences and difficulties in processing of CSF cytopathologic examination. Diagnosis of primary brain tumors based on CSF cytopathology has been challenging because of the low-yield processing techniques, the relatively small amount of CSF that is often obtained, the fragile character of the malignant cells, and low number of cells often

FIG. 6. Histopathologic examination of the biopsy specimen demonstrates abnormal cells with prominent nuclei, pseudopalisading and areas of necrosis. (Hematoxylin and eosin, 100×.)

FIG. 7. Glial fibrillary astrocytic protein stain (GFAP) of specimen shows diffuse staining in many cells. Vascular endothelial cell proliferation is evident. (GFAP, 100×.)
GLIOBLASTOMA MULTIFORME AND PTC

is extensive and must include brain tumors such as isodense gliomas, gliomatosis cerebri, lymphoma, and subarachnoid metastases, as well as infectious processes, inflammatory diseases, and arteriovenous malformations (5). In this particular case, the coincidental minocycline therapy obscured the underlying diagnosis. This case report emphasizes that PTC is a diagnosis of exclusion and should be considered in doubt when a patient develops an unusual course. A high index of suspicion, careful follow-up, and repeat studies are often necessary to reach a correct diagnosis.

REFERENCES


Cranial Neuropathy Heralding Otherwise Occult AIDS-Related Large Cell Lymphoma

Joseph R. Berger, M.D., Murray Flaster, Ph.D., M.D., Norman Schatz, M.D., David Droller, M.D., Pasquale Benedetto, M.D., Rita Poblete, M.D., and M. Judith Donovan Post, M.D.

Three HIV-infected patients developed cranial neuropathy as the initial manifestation of an AIDS-related large cell lymphoma. All were homosexual men known to be HIV seropositive for 3 to 4.5 years. At the time of presentation for neurological disease, the CD4 T-lymphocyte count was <400 cells/mm³ in each. Initial manifestations were retro-orbital headache and oculomotor nerve palsy in two and an abducens nerve palsy in the other. Repeatedly negative CSF cytologies and recovery of the cranial neuropathy obscured the diagnosis. These patients illustrate that cranial neuropathy with HIV infection may herald the presence of an occult large cell lymphoma. Spontaneous or corticosteroid-associated improvement of the cranial neuropathy, absence of abnormalities on brain imaging studies, and negative CSF cytologies do not exclude this diagnosis. We suggest that a diligent and repeated search for lymphoma be considered in HIV-infected patients presenting with cranial neuropathy, including repeated CSF examinations, MRI of brain and spine (T1 and T2) with and without gadolinium enhancement, chest and abdominal CT scans, and bone marrow biopsy.

Key Words: Human immunodeficiency virus, type 1—AIDS—Lymphoma—Cranial nerve disorders.

Approximately 9% of HIV-related neurological diseases are heralded by cranial neuropathy (1). The etiologies of cranial neuropathy occurring in association with HIV infection are diverse. Among the etiologies are infectious and neoplastic meningitides and mass lesions, inflammatory disorders, and vasculitis (1-14). Additionally, isolated and recurrent idiopathic Bell's palsy has been reported to occur in association with HIV infection (Table 1) (2,13,15,16), and multiple cranial polynyropathy has been observed at the time of HIV seroconversion (17). A review of cranial neuropathies occurring in 31 adults with the acquired immunodeficiency syndrome (AIDS) characterized 18 as multiple and 13 as single with the sixth and seventh cranial nerves most commonly affected (2). The etiologies of the cranial neuropathies were diverse and unexplained in 8 (26%) of the patients (2). Lymphoma was the etiology of the cranial neuropathy in 8 patients (26%) (2).

We report three HIV-infected patients who presented with cranial nerve disease as a consequence of HIV-related large cell lymphoma. At presentation, there were no other systemic or neurological manifestations. Radiographic imaging, including computed tomography (CT) of the brain and cranial magnetic resonance imaging (MRI) without gadolinium, were unremarkable. Cerebrospinal fluid (CSF) examination initially failed to reveal neoplastic cells. Prior to the establishment of the diagnosis, the presenting cranial neuropathy substantially improved or resolved in two patients. One patient had spontaneous resolution of his presenting abducens nerve palsy and another had near-total resolution of an oculomotor palsy following empirical corticosteroid therapy. The absence of abnormalities suggestive of lymphoma-
TABLE 1. The potential etiologies of cranial nerve palsies with HIV infection
(Adapted from reference 14)

<table>
<thead>
<tr>
<th>Infectious meningitis</th>
<th>Fungal</th>
<th>Cryptococcus</th>
<th>Histoplasmosis</th>
<th>Mucormycosis</th>
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</thead>
<tbody>
<tr>
<td>Bacterial</td>
<td>Mycobacterium tuberculosis</td>
<td>Listeria monocytogenes</td>
<td>Treponema pallidum</td>
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<tr>
<td>Viral</td>
<td>Herpes zoster/varicella</td>
<td>Cytomegalovirus</td>
<td>HIV meningitis</td>
<td></td>
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<tr>
<td>Neoplastic meningitis</td>
<td>Lymphoma</td>
<td>Other malignancies</td>
<td></td>
<td></td>
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<tr>
<td>Other malignancies</td>
<td>Compression from intracranial mass lesions</td>
<td></td>
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<tr>
<td>Neoplastic</td>
<td>Brain lymphoma</td>
<td>Other malignancies</td>
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<tr>
<td>Inflammatory</td>
<td>Toxoplasmosis</td>
<td>Cryptococcomma</td>
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<tr>
<td>Vasculitis</td>
<td>Tuberclulos and tuberculous abscess</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complicating HIV infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Guillain-Barré syndrome</td>
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<tr>
<td>Chronic inflammatory polyneuropathy</td>
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<tr>
<td>Miscellaneous</td>
<td>Malignant otitis externa</td>
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<td></td>
</tr>
<tr>
<td>Idiopathetic Bell's palsy</td>
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<tr>
<td>Other</td>
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</table>

tous meningitis and the clinical course of these patients resulted in a delay in the definitive diagnosis.

CASE REPORTS

Case 1

A 38-year-old bisexual man, documented to be HIV seropositive since May 1985, developed a left retro-orbital headache 1 week before hospitalization for presumed *Pneumocystis carinii* pneumonia in September 1988. While hospitalized, he noticed the onset of horizontal diplopia greater on leftward gaze and numbness of the right forearm, wrist, and thumb. The numbness persisted for 3 days, but shortly after its resolution he noticed right sciatic pain and severe pain in his left shoulder accompanied by a sensation of "hot grease" radiating into the fingers of the left hand. Examination revealed a left abducens nerve palsy. Chest x-ray, CT scan of the brain and orbits with and without contrast, cranial and cervical MRI, lumbar puncture with detailed microbiological studies and cytology, and gallium scan were unremarkable. The diplopia resolved within several weeks, but he noticed new difficulty raising his right arm. Past medical history was remarkable for hepatitis B 12 years earlier. The CD4 T-lymphocyte count was 109 cells/mm³, and the erythrocyte sedimentation rate was 88 mm/h.

Examination on November 28, 1988 revealed cervical adenopathy, left ptosis and pupillary dilation (left pupil measured 4 mm and the right 3 mm), partial left abducens and oculomotor nerve palsies, wasting and fasciculations of the left biceps and brachioradialis muscles, weakness of the opponens pollicis and abductor pollicis muscles, absent left biceps and brachioradialis muscle stretch reflexes, and decreased sensation in a left C6 dermatomal distribution. Laboratory studies were remarkable for a positive hepatitis B surface antibody and negative hepatitis B surface antigen. Repeat lumbar puncture showed an opening pressure of 15 cm of water, 0 WBC/mm³, protein 55 mg/dl, glucose 72 mg/dl, and nonreactive VDRL. CSF microbiological studies and cytology were again negative. An electromyogram and nerve conduction study were “consistent with a left brachial plexopathy with especially severe involvement of the lateral cord.” A muscle biopsy revealed evidence of “acute and chronic denervation” and a nerve biopsy showed “mildly abnormal changes favoring axonal degeneration and a single area of perivascular inflammation without true vasculitis.”

Oral prednisone, 20 mg three times daily, was initiated with improvement in the diplopia and numbness. Within 1 month, he developed severe left intercostal pain and numbness of the left groin followed by incontinence and difficulty walking. Examination on December 30, 1988, revealed normal mentation and cranial nerve function, weakness and atrophy of the left upper extremity, and a flaccid paraparesis with decreased sensation in the lower extremities, but no well-defined sensory level. An MRI of the lower thoracic and lumbar spine revealed multiple bony lesions involving the thoracic and lumbar spine and a large left paraspinal mass extending from T12 to L4 with involvement of the left psoas and erector spinae muscles. The cauda equina and conus medullaris were compressed by an epidural mass extending directly from the retroperitoneal lesion. An MRI-directed needle biopsy of the psoas mass revealed a large cell lymphoma. Radiation therapy (300 cGy daily for a total dose of 3,000 cGy) was initiated and dexamethasone (Decadron), 25 mg four times daily, was administered. He died on January 24, 1989. No vasculitis was observed at autopsy. There were no lymphomatous deposits in the meninges nor focal lesions of the spinal cord or cauda.
were normal.

Case 2

A 25-year-old homosexual man, HIV seropositive for 4.5 years, but otherwise healthy, developed the sensation of a foreign body in his right eye associated with an intermittent, right temporal headache in early July 1990, followed by the onset ptosis of the right eyelid. Within 5 days, he had developed a vertical diplopia that was worsened by gaze leftward and downward and was associated with complete right ptosis.

Examination revealed a complete right third nerve palsy sparing the pupil, but no stigmata of AIDS. Laboratory studies, cranial MRI, CSF examination with detailed microbiological studies and cytology, and cerebral angiography were unremarkable. Treatment with oral dexamethasone, 4 mg every 6 hours, was initiated with a gradual taper over 3 weeks. The patient experienced a prompt relief of his discomfort and marked improvement in the third nerve palsy.

Two weeks after discontinuing dexamethasone, he developed right facial paresis with discomfort in the right posterior cervical and postauricular regions. Examination revealed a slight adduction deficit of the right eye and a right peripheral facial palsy. Repeat cranial MRI with gadolinium and CSF examination were again negative. The facial weakness improved with oral prednisone, 40 mg daily.

One month later, he noted the onset of dysphonia and dysphagia. Examination revealed bilateral facial paresis, leftward deviation of the uvula, diminished gag reflex, flaccid dysphonia, weakness and atrophy of the left trapezius muscle, and a depressed right knee jerk. The absolute CD4 T-lymphocyte count was 485 cells/mm³. Chest x-ray was normal. A lumbar puncture showed an opening pressure of 18 cm of water, 160 white blood cells (86% mononuclear; 14% polymorphonuclear), protein 146 mg/dl, and glucose 32 mg/dl with a concomitant serum glucose of 137 mg/dl, IgG 11.0 mg/dl, and normal IgG index. The CSF microbiological studies, including stains, culture, VDRL, and cryptococcal antigen, were negative. CSF cytology was reported as "questionably abnormal." Five additional lumbar punctures, including a cisternal tap, during the ensuing 2 weeks were virtually identical, but failed to reveal abnormal cytology. Repeat cranial MR with gadolinium and CT scan of the chest, abdomen, and pelvis were normal.

Therapy for lymphomatous meningitis was initiated empirically, consisting of methotrexate, 10 mg intrathecally biweekly, and prednisone, 150 mg daily with gradual taper. Facial strength returned to normal and dysphonia and dysphagia improved. In October, the dysphagia and diplopia recurred with concomitant numbness of the left side of his face, left fingertips, and both feet. Examination showed right abducens and left trochlear nerve palsies, bilateral peripheral facial paresis, diminished gag reflex, flattening of the left side of the soft palate, increased weakness of the left trapezius muscle, weakness and wasting of the left deltoid, and sensory loss of the left face and fingertips. A bone marrow obtained in December 1990 showed infiltration by lymphoblasts and the chest x-ray a mass in the posterior sulcus. An Ommaya reservoir was placed for intrathecal methotrexate therapy and M-BACOD (methotrexate, bleomycin, dexamethasone, vincristine, and cytarabine) was initiated. CSF showed 6 WBC/mm³, protein 29 mg/dl, glucose 73 mg/dl, and negative cytology. A repeat cranial MR in January 1991, performed because of altered mental status revealed periventricular enhancement. He tolerated the chemotherapy well with partial remission of his cranial neuropathies over the next 5 months. He died on June 5, 1991. No autopsy was performed.

Case 3

A 37-year-old homosexual man, HIV seropositive for 4 years, presented on August 25, 1990, with severe right orbital pain and diplopia of 3 days duration. Examination showed right ptosis, anisocoria with the right pupil sluggishly reactive at 5.5 mm and the left briskly reactive at 3 mm, absent right eye adduction and elevation with limited depression, but preserved abduction and mild gait unsteadiness. Laboratory studies were remarkable for a hemoglobin of 10 g/dl and lactic dehydrogenase (LDH) of 1,689 U/ml. The chest x-ray was normal. A CT of the brain with double dose delayed contrast revealed only mild atrophy. MR angiography revealed no aneurysms. Lumbar puncture revealed clear colorless CSF with an opening pressure of 20 cm water, 0 RBC/mm³, 7 WBC/mm³ (100% mononuclear), protein 67 mg/dl, glucose 59 mg/dl, nonreactive VDRL, and negative microbiological studies and cytology. During the course of the hospitalization, he developed a right abducens nerve palsy and right hip pain with radiation into his thigh, and, subsequently, dyesthesias in a left L3-4 dermatomal distribution. Repeat
lumbar puncture revealed 3 RBC/mm³, 58 WBC/mm³ (100% mononuclear), protein 289 mg/dl, glucose 24 mg/dl. Microbiological studies and cytology were again negative.

Cranial MRI on September 18, 1990, revealed gadolinium enhancement of the tentorium (Fig. 1). Repeat lumbar puncture at that time showed 1,490 RBC/mm³, 24 WBC/mm³, protein 144 mg/dl, and glucose 40 mg/dl. All special studies including cytology were negative. The LDH remained elevated at 4,383 U/ml. One day later, he developed fever to 38.9°C. with jugular venous distension and a gallop rhythm. Chest x-ray revealed enlargement of the cardiac silhouette and echocardiogram confirmed a massive pericardial effusion with cardiac tamponade. Pericardiocentesis revealed an exudative fluid with 1,485 RBC/mm³, 3,114 WBC/mm³ (95% polymorphonuclear cells), protein 2,800 mg/dl, LDH >12,000 U/ml and specific gravity of 1.014. Cytology of the pericardial fluid showed cells consistent with a large cell lymphoma (Fig. 2). With systemic chemotherapy (cyclophosphamide, Adriamycin, vincristine, and prednisone) and radiation therapy directed to the base of his skull, his right oculomotor nerve and left abducens nerve palsies improved substantially. However, a stormy hospital course ensued, complicated by chylous fistula at the site of a central venous line, sepsis, and disseminated intravascular coagulation, and he died of cardiorespiratory arrest 7 weeks after his hospital admission. Permission for an autopsy was denied.

DISCUSSION

Cranial neuropathy heralded the presence of AIDS-associated systemic large cell lymphoma in these three patients. The remission of the cranial neuropathies (spontaneous in one and steroid-induced in another), the initial negative CSF cytologies, the normal radiographic imaging and the absence of systemic evidence of lymphoma obscured the diagnosis initially. One patient (Case 1) who presented with an abducens palsy and numbness of his right forearm and thumb that remitted spontaneously was at first considered to have a mononeuritis multiplex secondary to vasculitis. The correct diagnosis was not established until 3 months later, when an MRI showed thoracic and lumbar bone lesions and a paraspinous mass that proved to be lymphomatous. Mononeuritis multiplex secondary to vasculitis was also considered in another patient (Case 2) until repeat CSF examination revealed "questionably abnormal" cells. Despite a high index of suspicion, multiple subsequent CSF cytologies failed to demonstrate abnormal cytology. The diagnosis was not firmly established until a bone marrow biopsy was performed. The correct diagnosis was suspected in the third patient (Case 3) in light of his clinical presentation and increased serum LDH, but was not firmly established until he developed a lymphomatous pericardial effusion 1 month after presentation.

Approximately 5% of patients with AIDS develop lymphoma (18). Non-Hodgkin’s lymphoma is estimated to be 60 times more common in AIDS patients than in the general United States population (19). Lymphomas associated with AIDS may be systemic or arise within the central nervous system. The typical presenting manifestations of systemic lymphomas include the appearance of a rapidly growing mass lesion or the development of type B systemic symptoms, including unexplained fever, drenching night sweats, and weight loss (20). AIDS-related systemic lymphoma, however, is characterized by a high frequency of extranodal disease at the time of presentation. The incidence of the latter is reported at 56% to 86%, rates substantially higher than that seen with systemic lymphoma occurring in the general popula-

FIG. 1. Cranial magnetic resonance image of Case 3. Contrast-enhanced T1-weighted coronal image (repetition time: 750 ms; echo time: 20 ms) showing subtle enhancement along the tentorium (arrowhead).
A central nervous system presentation occurs in approximately one-third of AIDS-related lymphomas (18). The most common form of presentation is lymphomatous leptomeningitis, which may be either asymptomatic or symptomatic. In an AIDS Clinical Trials Group study of AIDS-related lymphoma in which lumbar puncture was mandated by protocol, 17% of patients had unsuspected neoplastic cells in the CSF (18). In 67 HIV-infected patients with systemic, non-Hodgkins lymphoma, 14 had involvement of the meninges, 5 had either cranial or peripheral nerve involvement, and 5 had paraspinal masses (21).

Clinical features of symptomatic lymphomatous leptomeningitis include headache, altered mental status, seizures, cranial neuropathies, and radiculopathies. Cranial neuropathy may be the presenting manifestation of malignant lymphoma (22). In one study of 24 patients with cranial neuropathy due to lymphomatous leptomeningitis unassociated with AIDS, the most commonly involved cranial nerves were the facial, oculomotor, and abducens (23). Complete resolution of cranial neuropathy due to meningeal lymphoma following therapy (24) as well as spontaneous remission have been reported (25).

The direct spread of lymphoma cells into the central nervous system (CNS) from contiguous extraneural sites has been suggested as the most common mode of entry (26). The high frequency of lymphomatous bone marrow infiltration that occurs in association with lymphomatous leptomeningitis (26-29) suggests that the malignant cells enter from the medullary cavity through the dura and into the subarachnoid space (26).

Because cranial neuropathy in an HIV-infected patient may herald an otherwise occult systemic lymphoma, we strongly recommend that a diligent and repeated search for lymphoma be considered in patients with otherwise unexplained cranial neuropathies, particularly when associated with an elevated serum lactic dehydrogenase (30). Repeated CSF examinations with immunocytochemical studies (31) are mandated due to the difficulty in distinguishing reactive lymphocytes from lymphoma cells. Plain and gadolinium-enhanced MRI of brain and spine (T1 and T2) need to be obtained and chest and abdominal CT scans should be considered in order to detect the presence of extra-CNS disease. As bone marrow infiltration is frequently observed in association with lymphomatous invasion of the CNS (23), bone marrow biopsy may be particularly helpful in detecting a lymphoma that has invaded the subarachnoid space.

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FIG. 2. Cytopathology of pericardial fluid of Case 3. Pericardial fluid showing cells consistent with large cell lymphoma (Pap stain).
Bilateral Isolated Retrobulbar Optic Neuropathy in Limited Wegener's Granulomatosis

Clifford J. Belden, M.D., Latif M. Hamed, M.D., and Anthony A. Mancuso, M.D.

Wegener's granulomatosis causes a variety of ophthalmologic disorders, some of which occasionally constitute the initial presentation of the disease. We describe a patient who presented with bilateral, isolated, consecutive, posterior optic neuropathy with light perception and no light perception vision. The patient had no other symptoms or signs of orbital disease. Investigations revealed cavitary lung lesions, positive antineutrophilic cytoplasmic antibody (ANCA) titers, subtle focal enhancement of the intracanalicular optic nerves on magnetic resonance imaging, and a confirmatory bronchial biopsy. This exceedingly rare ocular presentation of Wegener's granulomatosis may pose a diagnostic quandary.

**Key Words:** Optic neuropathy—Wegener's granulomatosis—ANCA.

CASE REPORT

A 55-year-old woman was referred to our institution with the diagnosis of bilateral consecutive optic neuropathy. The patient had been well until approximately 1 year previously when she began having sinus congestion and pressure. At 9 months prior to admission she had an episode of "colitis" associated with a purpuric rash on her lower extremities with non-tender nodules over her ankles, knees, and elbows. The colitis required hospitalization and multiple transfusions. A colonic biopsy revealed "vasculitis." She was treated with prednisone with resolution of her symptoms. The prednisone was slowly tapered over the next 6 months, and a repeat colonoscopy showed no evidence of colitis.

At 6 weeks prior to admission the patient noted a central scotoma in her left visual field with reduced vision. This reportedly cleared spontaneously over the next week, but then recurred, at which time she sought an ophthalmologic evaluation. Vision was decreased in the left eye to hand
motions with an afferent pupillary defect. Westergren sedimentation rate was 32 mmHg. She was begun on oral prednisone, 10 mg daily. A spinal tap revealed 1 WBC, 111 RBC, glucose of 65 mg%, and protein of 52 mg%. Myelin basic protein and oligoclonal bands were absent. Cerebral spinal fluid IgG synthesis was mildly elevated at 4.25 mg/24 hours. Cerebral spinal fluid cultures, cryptococcal antigen, toxoplasmosis IgG antibody, and VDRL were negative.

The patient lost vision in the right eye 14 days later, to the level of counting fingers. She was admitted to the hospital with a diagnosis of bilateral optic neuritis and Solu-Medrol, 500 mg intravenously, was administered daily for 5 days. Her vision improved slightly, and she was discharged on no corticosteroids. Her vision remained stable for several days, then slowly decreased over the next 3 to 4 days. She was referred to our institution 9 days after discharge, when she awoke and could not see light with either eye.

The patient complained of continuing sinus pressure and mild left periorbital discomfort. There was no pain on ocular movement. No known toxic exposures had occurred, and she denied tobacco and alcohol use. Past medical history was significant for B12 injections, Ouricef, and iron. Family history was noncontributory.

On examination, vision was light perception in the right eye and no light perception in the left. Pupils were 6 mm each, with a trace reaction to light bilaterally, without a relative afferent defect. There was no proptosis or any other sign of orbital involvement. Applanation tensions were normal. Results of slit lamp and dilated funduscopic examinations were normal. Specifically, the optic discs showed no edema, hemorrhages, or pallor.

The patient was admitted for intravenous Solu-Medrol, 250 mg every 6 hours. Further workup included a chest radiograph, which revealed bilateral apical infiltrates, right greater than left, with a differential diagnosis, including tuberculosis and Wegener's granulomatosis (Fig. 1). A PPD (purified protein derivative) skin test was placed along with controls, and the results revealed the patient to be anergic. Because tuberculosis could not be ruled out, INH (isoniazid) and rifampin were begun orally. Magnetic resonance imaging of the orbits with gadolinium and fat suppression revealed bilateral subtle enhancement of the intracanalicular optic nerve sheaths with contiguous enhancement of the dura overlying the cavernous sinus (Fig. 2A). The intraorbital and intracranial portions of the optic nerves, as well as the optic chiasm and tracts appeared normal.

Laboratory evaluation was significant for a white blood cell count (WBC) of 9,700/mm³, and microcytic anemia with a hematocrit of 30.2%. Electrolytes, liver function tests, urinalysis, PT, and PTT were all normal. Westergren sedimentation rate was elevated to 72 mm/h, and C3 and C4 complement levels were mildly elevated. HATTS, VDRL, rheumatoid factor, antinuclear antibodies, and Lyme titers were negative.

An otolaryngologic examination revealed ulceration of the nasal septum, and a biopsy revealed squamous mucosa with acute and chronic inflammation and scale crust formation. An initial transbronchial biopsy revealed no significant vasculitis, granulomas, or inflammation.

![FIG. 1. Admission chest radiograph demonstrating biapical infiltrates, with the right greater than the left. No cavitation is evident. These infiltrates were more extensive than those on a comparison film from 8 months previously.](image-url)
FIG. 2. (A) Magnetic resonance image obtained on the patient’s first admission with subtle enhancement of the optic nerve sheaths (arrow) and dura overlying the cavernous sinus (arrowheads); all findings are more prominent on the right. (B) On the patient’s second admission, a repeat magnetic resonance imaging study again revealed enhancement of the intracanalicular optic nerve sheaths (arrow) as well as enhancement of the dura just anterior to the cavernous sinus on the right (arrowheads) and planum sphenoidale (open arrow).

The patient was continued on high-dose intravenous corticosteroids for 10 days with slow improvement in her vision to count fingers in both eyes. She was discharged on Medrol, 48 mg per day orally, as well as antituberculosis medications.

Two weeks later the patient awoke with her vision decreased to light perception in the right eye and hand motion in the left. She was again admitted and placed on Solu-Medrol 250 mg every 6 hours. The antineutrophilic cytoplasmic antibody (ANCA) sent to the laboratory on her previous admission returned positive at 52 units (<22 units is negative; Specialty Laboratories Inc., Santa Monica, CA). The following day Cytoxan therapy was begun intravenously. Her vision improved to count fingers bilaterally over the next 2 days. A repeat magnetic resonance imaging study of the orbits again revealed enhancement of the intracanalicular optic nerve sheaths bilaterally and enhancement of the planum sphenoidale and meninges overlying the cavernous sinus on the right (Fig. 2B).

The patient was discharged, and Medrol, orally 16 mg three times a day, was prescribed. Vision continued to improve slowly. On follow-up she was noted to have increases in cough, sputum, and some hemoptysis. A chest radiograph revealed increased cavitation in the right upper lobe. The patient was admitted for antibiotics intravenously. A repeat bronchoscopy was performed and a 0.5-mm lesion was seen intrabronchially and biopsied. Pathologic examination revealed necrotizing granulomatous vasculitis consistent with Wegener’s granulomatosis.

Over the next 2 months the patient was maintained on oral Medrol and Cytoxan with maintenance of her vision at the level of count fingers bilaterally. A repeat antineutrophilic cytoplasmic antibody titer (ANCA), taken 3 months after the original, had decreased to 30 units.

**DISCUSSION**

Wegener’s granulomatosis is a systemic necrotizing granulomatous vasculitis (1) with frequent ophthalmologic (2,3,7,8) and neurologic manifestations (10,11). It occurs in a classic form with involvement of lungs, sinuses, and kidneys, and in a
limited form that spares the kidneys and has an overall better prognosis (4,12,13). Ocular involvement may be the presenting complaint in Wegener’s granulomatosis, particularly in the limited form of the disease (6,7). Ocular involvement generally is of two varieties—focal and contiguous. Focal disease occurs independent of respiratory tract involvement and frequently involves sclera, episclera, cornea uvea, and retina. Contiguous disease results from direct spread of inflammation from surrounding sinuses and is manifest by orbital inflammation (2-4,7,8).

Our patient had some atypical features of Wegener’s granulomatosis that made the diagnosis more difficult. Initially, the presence of ulcerative lesions in the nasal cavity and tracheobronchial tree was suggestive of Wegener’s granulomatosis, but the location of the cavitary lung lesions in the upper lobes was somewhat unusual, suggesting the possibility of tuberculosis. The case for Wegener’s was strengthened when the antineutrophilic cytoplasmic antibody (ANCA) was positive. The history of colitis and purpura occurring 9 months prior to the visual loss strengthened the case for a vasculitic disorder. It is tempting to speculate that had a diagnosis been made at that time and appropriate therapy instituted, the visual loss might have been averted. Our clinical suspicion for Wegener’s granulomatosis remained despite the initial nondiagnostic biopsies, partially due to the positive ANCA, leading to the second, confirmatory biopsy. Recent studies have documented the usefulness of ANCA for the workup of suspected vasculitic disorders of the eye (14).

It should be emphasized that the initial monocular visual loss in our patient should have inspired a complete workup for giant cell arteritis, even though the patient is at the younger end of the spectrum for the condition. This is of obvious importance so that appropriate therapy may be initiated within the narrow window of opportunity between unilateral and consecutive visual loss.

The optic nerve is the most commonly affected cranial nerve in Wegener’s granulomatosis (15), and may become involved either as a result of orbital disease with resultant compression, or because of inflammation of vessels supplying the optic nerve (4,5,7-9).

In a 1957 review of ocular complications of Wegener’s, Straatsma (3) describes one patient who developed decreased vision and proptosis who on autopsy had encasement of the nerve with necrotic granuloma, but with preservation of the nerve substance.

In a review of 140 patients with Wegener’s granulomatosis, Bullen et al. (2) found 9 patients with optic nerve involvement; 6 of these were due to contiguous orbital disease, but 3 had no evidence of orbital disease. Unlike our patient, all three had optic disc swelling (2).

Spalton (7) described eight patients with the limited form of Wegener’s granulomatosis, all of whom had ocular involvement. Four of these patients had orbital disease, and one developed bilateral optic neuropathy from compression of the optic nerves by a parasellar mass (7).

In the review of Haynes et al. (8), of 29 patients with Wegener’s granulomatosis, 4 developed vasculitic involvement of the optic nerve. All 4 patients showed proptosis; 2 of these had vision of no light perception at presentation, and 1 recovered 20/20 vision after treatment with corticosteroids and Cytoxan (8).

Anderson et al. (15) described a patient who developed bilateral consecutive loss of vision with normal findings on funduscopy. At craniotomy a layer of abnormal tissue over the anterior fossa and encasing the optic nerves was found. On histology there was chronic inflammation and multinucleate giant cells, but no evidence of vasculitis (15).

The radiographic finding in our patient of enhancement of the meninges in the anterior cranial fossa and optic nerve sheaths may represent a similar process. The pattern of dural enhancement contiguous with the optic nerve sheath and sparing of the nerve both anterior and posterior to this area suggest primary involvement of the meninges with Wegener’s granulomatosis and secondary involvement of the optic nerves.

Acute isolated consecutive retrobulbar optic neuropathy has been rarely described either as a presenting sign or accompanying Wegener’s granulomatosis at any stage. We could find only one brief citation, provided by Miller (16), of a case apparently similar to ours, but as the details of the case are lacking, the status of orbital involvement is unknown (17). Our patient demonstrates that optic neuropathy associated with Wegener’s disease may pose a diagnostic quandary. Absence of signs of orbital inflammation and absence of optic disc swelling in the setting of acute consecutive bilateral optic neuropathy has been rarely reported in Wegener’s disease and initially suggested posterior ischemic optic neuropathy due to giant cell arteritis.

REFERENCES

OPTIC NEUROPATHY IN WEGENER'S GRANULOMATOSIS

Intermittent Third Nerve Palsy with Cryptococcal Meningitis

James R. Keane, M.D.

In the several days before death, two AIDS patients with cryptococcal meningitis and increased intracranial pressure (ICP) experienced episodic unilateral third nerve palsies seemingly related to transient peaks in ICP. While cryptococcal neuritis may have predisposed the nerves to pressure effects, CT scans showed no evidence of tentorial herniation. These cases raise the possibility that severe elevations of ICP can precipitate third nerve paresis on rare occasions.

Key Words: Third nerve palsy—Cryptococcal meningitis—Increased intracranial pressure—AIDS.

Meningitis is a well-recognized cause of third nerve damage. Possible mechanisms include direct invasion or vasculitic infarction of the nerve, midbrain infarction and abscess, and tentorial herniation. The following patients with terminal cryptococcal meningitis showed unusual intermittent oculomotor nerve pareses that appeared to be related to increased intracranial pressure (ICP) in the absence of tentorial herniation.

CASE REPORTS

Case 1

A 21-year-old man with acquired immunodeficiency syndrome (AIDS) was admitted following 2 weeks of headache. Physical examination was normal, aside from elevated blood pressure, and his computed tomographic (CT) scan showed no abnormalities. Lumbar puncture results included a resting pressure of 370 mm cerebrospinal fluid, no cells, a protein value of 20 mg/dL, and a glucose level of 50 mg/dL. Cryptococci were seen on India ink preparation, cerebrospinal fluid cryptococcal antigen titers were positive, and amphotericin therapy was begun.

Two days after admission, he experienced a sudden increase in headache severity, became lethargic, and developed severe left third nerve paresis. Repeat CT scan was again read as normal, but showed mild diffuse cerebral swelling when carefully compared to the initial and subsequent studies. Within minutes of administering intravenous mannitol, the third nerve palsy disappeared. On two further occasions in the next 36 hours a complete isolated left third nerve palsy with a 6-mm fixed pupil appeared and resolved within 30 minutes after mannitol administration. In the following 12 hours he became progressive obtunded and died.
Case 2

A 34-year-old AIDS patient was admitted because of 3 weeks of headache, myalgias, and weight loss. Eye movements and pupillary functions were normal, but papilledema was present.

Early the next morning, following sedation with morphine in the emergency room, he developed a third nerve palsy manifested by a dilated, fixed pupil and severe ptosis. These signs cleared as the effects of the morphine wore off, but later that morning he became transiently obtunded with increased headache and right ptosis, a 7-mm fixed right pupil, and a 4-mm fixed left pupil. An enhanced CT scan was normal. That afternoon, a third episode of severe right third nerve paresis manifested by right ptosis, nearly complete adduction paresis (vertical movements could not be assessed) and a 6-mm fixed pupil (left pupil 3 mm and reactive) was accompanied by difficulty seeing and hearing and increased lethargy. The episodes lasted from 15 to 40 minutes.

A lumbar puncture showed a resting pressure greater than 550 mm cerebrospinal fluid, 16 monocytes, a protein value of 34 mg/dL, and a glucose level of 37 mg/dL. Budding yeast was abundant on Indian ink preparation and Cryptococcus neoformans later grew from multiple cultures. Treatment with amphotericin and dexamethasone was initiated. The patient became progressively obtunded and experienced a cardiac arrest 40 hours after arriving at the hospital.

DISCUSSION

Third nerve palsies develop in varying patterns; most advance steadily to a maximum, many show saltatory progression, and a few demonstrate spontaneous temporary improvement. Repeated rapid development of a severe third nerve palsy followed by resolution within the hour, as seen in our patients, is a highly unusual event.

Cryptococcal meningitis, a common secondary infection in AIDS, is often associated with marked elevations in ICP (1,2). The three 10- to 40-minute episodes of severe third nerve paresis that each of our patients experienced were accompanied by increased headache and mild to severe obtundation. Most episodes coincided with events that suggest fluctuations in intracranial pressure: morphine precipitation, relief after mannitol, and simultaneous obtundation with hearing and visual loss similar to symptoms seen with plateau waves (3). In one episode, the opposite pupil was smaller but also fixed, suggesting midbrain involvement in that instance. CT scans of both patients were obtained at the time of the episodes and eliminated tentorial herniation as a cause of the oculomotor nerve palsy.

Increased intracranial pressure (IICP) is not an accepted cause of oculomotor nerve paresis. Third nerve damage associated with tentorial herniation is sometimes loosely said to be due to “pressure,” but the proximate cause is brain shift and compression of the third nerve and midbrain. The experimental Cushing response to IICP may include late serial pupillary dilation, but the effects of midbrain distortion and terminal midbrain ischemia confound any possible direct effect of pressure upon the third nerve (4,5). Similarly, in older reports of third nerve palsies associated with remote intracranial tumors (6), the effects of brainstem distortion and meningeal tumor spread cannot be discounted.

Benign intracranial hypertension (BIH) provides the purest clinical example of IICP. Abducens nerve palsies are commonplace, but rare involvement of other cranial nerves has been reported with benign intracranial hypertension. Reports of possible third and fourth nerve palsies include instances of diffuse ophthalmoplegia of uncertain localization and patients with minor vertical diplopia which may be secondary to the horizontal dissociation from abducens pareses (7). However, a case of apparent benign intracranial hypertension, (8) in which a complete third nerve palsy was preceded by episodic pupillary dilation and decerebrate posturing, suggests that pressure-induced midbrain and oculomotor effects might have occurred in that patient.

Rapid fluctuations of sixth nerve function, similar to the intermittent third nerve pareses in our patients, have been observed in a case of cryptococcal meningitis with severe IICP (9). The 5- to 15-minute episodes of bilateral abducens pareses in that patient were accompanied by headache, obtundation, tinnitus, decreased hearing, facial sagging, a sluggish response in one or both pupils, and an elevation in blood pressure, suggesting a brainstem effect of transient intracranial pressure elevation (3,4).

That the intermittent third nerve pareses in our two patients were strictly the result of IICP is unlikely; predisposing infectious invasion of the nerves was probably present. However, the episodes are unusual in themselves and raise the possibility that, under exceptional circumstances, elevated ICP may precipitate third, as well as sixth, nerve pareses.
REFERENCES


Idiopathic Hypertrophic Cranial Pachymeningitis

Steven R. Hamilton, M.D., Craig H. Smith, M.D., and Simmons Lessell, M.D.

We evaluated 3 patients with biopsy-proven hypertrophic cranial pachymeningitis apparently unrelated to any systemic disease. Each patient had chronic headache, cranial neuropathy, an elevated ESR, and a mild CSF pleocytosis. Neuro-ophthalmic findings included bilateral sixth nerve palsies in two patients and the third had bilateral optic neuropathies. MR imaging revealed thickened dura that enhanced with Gd-DTPA administration. Histologic examination showed thickened, fibrotic dura with a sterile, chronic, nongranulomatous inflammation. The response to treatment was variable with corticosteroids, immunosuppressive drugs, or radiation. The distinctive MR appearance should help physicians recognize this rarely reported disease.

Key Words: Pachymeningitis—Dura—Magnetic resonance imaging.

Dural thickening may be caused by syphilis, tuberculosis, sarcoidosis, rheumatoid arthritis, metastatic carcinoma, meningioma, fibroma, and extension of inflammatory orbital pseudotumor (1,2). We present the findings in three cases of a rare disorder termed idiopathic hypertrophic cranial pachymeningitis in which magnetic resonance (MR) imaging uniformly revealed thickened dura that enhanced strikingly after Gd-DTPA (gadolinium-diethylenetriamine pentaacetic acid) administration. In all cases biopsy demonstrated a sterile, chronic, nongranulomatous inflammation of thickened, fibrotic dura.

CASE STUDIES

Case 1

A previously healthy 55-year-old white woman developed intermittent headaches in 1980. By 1984 the headaches had become more frequent and were predominantly right-sided. An evaluation at that time revealed an erythrocyte sedimentation rate (ESR) of 90 mm/h, which prompted a temporal artery biopsy. Although the biopsy was negative, oral prednisone therapy was initiated, and she required 60 mg/day of prednisone during the next 3 years to control the headache. In 1986 she developed tongue spasms precipitated by head turning, which responded to Dilantin therapy. Prednisone was gradually tapered off in 1987–1988 with only occasional headaches, but she remained on Dilantin until 1990.

In July 1990 the patient developed diplopia on right gaze with brief episodes of paroxysmal headache. An ophthalmologist found limitation of ab-
duction of the right eye. General medical and pulmonary evaluations were unrevealing despite an ESR of 85 mm/h. Serum RPR and FTA-ABS tests were nonreactive, while her chest radiograph and serum angiotensin-converting enzyme (ACE) level were normal. Computed tomography (CT) of the brain and orbits showed marked enhancement of the tentorium. The cerebrospinal fluid (CSF) opening pressure was 225 mm CSF with 6 white blood cells/mm$^3$ (3 polymorphonuclear cells and 3 monocytes), 86 mg% protein, and 55 mg% glucose. She was treated with oral dexamethasone (Decadron) which improved, but failed to eliminate, her symptoms. An MR scan of the brain (Fig. 1) demonstrated diffuse meningeal thickening, which enhanced after the administration of Gd-DTPA. No abnormalities were noted on a 4-vessel cerebral angiogram.

In November 1990 the brain and meninges were biopsied via a right frontal craniotomy. Fibrous thickening of the dura exceeded 2 mm in several areas. The dura contained a patchy nongranulomatous inflammatory infiltrate consisting of lymphocytes and occasional plasma cells (Fig. 2). The cerebral cortex and all blood vessels appeared normal. Stains for bacteria, fungi, mycobacteria, nocardia, spirochetes, and protozoa were negative.

Despite high-dose corticosteroid treatment, she continued to have severe headaches. When the corticosteroid dose was reduced she developed a left sixth nerve palsy. Azathioprine was substituted for prednisone in July 1991, and within 6 months her headache and tongue spasms had ceased, normal motility was restored to the left eye, and there was improved abduction of the right eye.

Case 2

A 68-year-old previously healthy white woman presented in July 1989 with fever, lethargy, bilateral hearing loss, nonproductive cough, sore throat, and mandibular pain. There was neither headache nor visual impairment, but she had one brief episode of binocular diplopia. Ophthalmologic, general physical, and neurological examinations gave unremarkable results. The total white blood count was 15,000/mm$^3$, hematocrit 30%, platelet count 715,000/mm$^3$, and ESR 95 mm/h. Temporal artery biopsy showed granulomatous inflammation. Oral corticosteroid treatment rapidly relieved all of her symptoms.

Several months later the patient complained of blurred vision in the left eye. However, neuroophthalmic examination in December 1989 showed only slight posterior subcapsular cataracts, and fluorescein fundus angiography was unrevealing. Over the next month vision failed to 20/70 in her left eye with dyschromatopsia and an upper altitudinal visual field defect. The fundi were unremarkable, and her ESR was 3 mm/h. Visual function promptly recovered when her prednisone dose was increased to 80 mg/day. However, when the dose was reduced to 60 mg/day, vision again declined. CT of the brain and orbits with contrast was normal. Over the succeeding months she continued to manifest visual loss in the left eye that could only be reversed with 60 to 100 mg/day of

![FIG. 1. MR imaging of case 1. T1-weighted (TR = 600 ms, TE = 15 ms) right parasagittal images (A) before and (B) after Gd-DTPA. There is prominent thickening and enhancement of the tentorium cerebelli as well as the occipito-parietal dura.](image)
IDIOPATHIC HYPERTROPHIC CRANIAL PACHYMENINGITIS

FIG. 2. Sections from the dural biopsy in Case 1. (A) At low magnification the dura is thickened and fibrotic, while (B) higher magnification reveals a chronic inflammatory infiltrate consisting of lymphocytes and plasma cells. Hematoxylin and eosin. Bar = 200 μm at low magnification, and 40 μm at high magnification.

prednisone. Even on this dose there was dyschromatopsia and a left relative afferent pupillary defect. Her left optic disc became pale. Throughout this period, the ESR remained in the single digits and fibrinogen levels were normal.

By May 1990 vision in the left eye was 20/25 and declined to 10/200 over the next month. Evaluation by a retinal consultant, fluorescein fundus angiography, and CT of the orbits in June 1990 failed to explain her progressive visual failure. In November 1990 the visual acuity in the right eye had declined to 20/30 because of a cataract. An MR scan with Gd-DTPA and a contrast-enhanced CT scan now demonstrated a lesion in the apex of the left orbit. The appearance was considered most compatible with a meningioma.

Uncomplicated extracapsular cataract surgery was performed on the right eye in April 1991, but
vision in the right eye declined to hand motions perception during the immediate postoperative period. Her right fundus was unremarkable. The ESR was normal, but C-reactive protein was positive and fibrinogen was mildly elevated at 418 mg% (normal 200–400 mg%). With the institution of 120 mg/day of prednisone vision rapidly improved to 20/40 and color vision (Ishihara) returned to normal, but there was a temporal visual field defect.

An MR scan demonstrated enlargement and enhancement of the apical end of the intraorbital segment of the left optic nerve. Other orbital structures, the optic chiasm, and right optic nerve appeared normal. Coronal images revealed marked Gd-DTPA enhancement of the meninges of the left anterior cranial fossa crossing the midline to the right side (Fig. 3). The CSF opening pressure was 120 mm and contained 9 white blood cells/mm³ (3 polymorphonuclear cells and 6 monocytes), 61 mg% glucose, and 49 mg% protein. Cytological examination for malignant cells, routine bacterial, fungal, and acid fast bacillus (AFB) cultures, and CSF VDRL were all negative. Apical scarring and calcified hilar lymph nodes were seen on chest radiographs but there was no evidence of active pulmonary disease. Serum RPR, FTA-ABS, rheumatoid factor, antinuclear cytoplasmic antibody (ANCA) level, ACE level, and lysozyme all gave normal results.

In May 1991 the meninges were biopsied via a left frontal craniotomy. The dura over the floor of the anterior cranial fossa was markedly thickened. Microscopic examination of the meninges and cerebral cortex demonstrated a multifocal, nongranulomatous, chronic inflammatory infiltrate of the dura consisting of lymphocytes with occasional plasma cells. Blood vessels were not involved. Stains for bacteria (including AFB), fungi, nocardia, spirochetes, and protozoa were negative.

The patient has subsequently been maintained on oral prednisone and azathioprine. Visual acuity in November 1992 was 20/15 right eye with normal color vision and a temporal paracentral scotoma.

**Case 3**

A 31-year-old, previously healthy, white man developed paroxysmal, holocephalic nonthrob- bing headaches unresponsive to aspirin in 1987. These continued, and 2 years later he noticed bino­cular horizontal diplopia. Neuro-ophthalmic examination in October 1989 showed partial limita­tion of abduction of the left eye. A complete blood count, blood glucose determination, thyroid function tests, acetylcholine receptor antibody test, Lyme antibody titer, RPR and FTA-ABS, and antinuclear antibody titer were all within normal limits. The ESR was 4 mm/h. A nonenhanced MR scan of the brain was unremarkable. His headaches and the abduction deficit cleared spontaneously in 6 weeks.

In October 1990 the horizontal diplopia returned accompanied by left hemicranial pain. Neurological examination showed an impaired tandem gait and a right lateral rectus muscle paresis. Neuroimaging with Gd-DTPA (Fig. 4) revealed diffuse enhancement of the basal meninges, including the cavernous sinuses and suprasellar region. Endocri­nological evaluation documented hypothyroidism and a low serum testosterone level. His ESR was 27 mm/h. An ACE level was within normal limits, and a test for HIV was negative. His CSF opening pressure was normal with 9 white blood cells/mm³ (2% polymorphonuclear cells, 85% lymphocytes, 13% histiocytes and monocytes), 55 mg% glucose, and 71 mg% protein. Cytological examination showed no malignant cells and stains and cultures for AFB were negative. An extensive pulmonary evaluation with two transbronchial biopsies and biopsies of an axillary lymph node, the lip, tongue, and conjunctiva failed to show evidence of dis­ease.

He was treated for 1 year with daily prednisone doses of 20–60 mg. When depression and obesity
IDIOPATHIC HYPERTROPHIC CRANIAL PACHYMENINGITIS

FIG. 4. MR imaging of Case 3. A T1-weighted (TR = 700 ms, TE = 20 ms) coronal image after Gd-DTPA shows regional enhancement of the basal meninges, as well as the cavernous sinuses and suprasellar region.

necessitated tapering of the prednisone, he suffered increased diplopia and left orbital pain. An MR scan with Gd-DTPA showed further thickening of the meninges. The left internal carotid artery, encased by the process in the cavernous sinus, appeared occluded. Cerebral angiography confirmed the MR findings and suggested encasement of the right intracavernous carotid artery as well, but there were no other lesions. A trial of methotrexate was aborted after 6 weeks because he developed tongue ulcers and there had been no beneficial response.

Biopsy of the brain, meninges, and cavernous sinus in December 1991 revealed thickened dura with multiple foci of chronic, nongranulomatous inflammation. Cultures for fungi, bacteria, and AFB were negative. Chloroquine therapy was started, and the patient also received 4,500 cGy of whole-brain radiation. Two months later his pain was much improved, and ocular motility was normal. However, he had several 15-minute episodes of right arm and leg weakness with numbness accompanied by mild left hemicranial headache. The transient ischemic attacks subsequently resolved within 4 months on chloroquine therapy.

DISCUSSION

In 1989 Martin et al. (1) called attention to the existence of cases of idiopathic hypertrophic cranial pachymeningitis. The three patients in their series presented with chronic headaches with an elevated ESR accompanied by ataxia or palsies involving cranial nerves 7, 8, 10, or 11. Contrast-enhanced CT or MR imaging (without Gd-DTPA) demonstrated tentorial thickening, which enhanced with contrast. A common pathology consisted of a thickened, fibrotic dura with a chronic inflammatory infiltrate with no evidence of arteritis. All patients eventually received both corticosteroid and azathioprine therapy, but only one enjoyed resolution of symptoms. One patient received whole-brain radiation without improvement. The same three cases were presented in the same year in the French literature by Masson et al. (3). Willing and Broghamer (4) recently reported a 35-year-old man with headaches, a right abducens nerve palsy, and an enhancing mass seen with cranial MR imaging in the sella and cavernous sinuses that encased the carotid arteries similar to our third case. Transsphenoidal biopsy revealed dense collagen with focal fibroplasia and inflammatory cells consistent with idiopathic cranial pachymeningitis.

Our cases of idiopathic hypertrophic cranial pachymeningitis corroborate many of the findings described by Martin et al. (1), while further defining the clinical profile, MR appearance, and response to therapeutic intervention. Table 1 summarizes the features in our cases as well as in the other cases reported in the English literature. Patients commonly present with chronic headache accompanied by symptoms that include either ataxia, blindness, or palsies involving cranial nerves V through XII. Neuro-ophthalmic complications include papilledema, optic neuropathy secondary to inflammation or compression, and sixth nerve palsies. While the disorder does not appear to be systemic, with clinical and imaging abnormalities limited to the nervous system, an elevated ESR is often present. The significance of the association with chronic renal failure in two cases and temporal arteritis in another remains uncertain given the limited number of reported cases. MR imaging with Gd-DTPA, as seen in our three patients, demonstrates a very characteristic pattern of either regional or diffuse dural thickening with enhancement. Our patients showed a more widespread pattern of dural thickening than the cases presented by Martin et al. (1) in which the falx and tentorium were involved. Biopsy of the involved dura revealed thickened, fibrotic dura with a sterile, multifocal, chronic inflammatory infiltrate without evidence of either vasculitis or malignancy. Both our cases and those reported by Martin et al. (1) have been nongranulomatous, although in Table 1 the cases described by Feringa
and Weatherbee (5) and Kobayashi et al. (6) did contain granulomas. Attempts at therapeutic intervention in these small numbers of patients have yielded highly variable responses to corticosteroids, immunosuppression, and whole-brain radiation.

Pachymeningitis cases have previously been attributed to syphilitic, mycobacterial, and fungal infections of the central nervous system. In the era before computed tomography, syphilis and tuberculosis were the infectious agents most frequently cited (7,8). The diagnosis rested almost entirely upon the pathologic findings, which often included gumma formation and evidence of an endarteritis, as in the case reported by Hassin and Zeitlin (7). Nevertheless, 2 of the 4 cases described in the French literature by Michel et al. (8) in 1969 were assumed to be noninfectious or of idiopathic

### TABLE 1. Cases of idiopathic hypertrophic cranial pachymeningitis in the English literature

<table>
<thead>
<tr>
<th>Author (ref.)</th>
<th>Pt. no. (age/sex)</th>
<th>Clinical findings</th>
<th>MRI/CT findings</th>
<th>ESR/ temporal artery biopsy</th>
<th>Pathology</th>
<th>Medical therapy</th>
<th>Clinical response</th>
<th>Systemic conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feringa &amp; Weatherbee, 1975 (5)</td>
<td>1 (50/M)</td>
<td>Bilateral optic neuropathy</td>
<td>None</td>
<td>64/none</td>
<td>Thick dura with chronic inflammatory infiltrate, granulomas</td>
<td>None</td>
<td>Progression</td>
<td>Chronic renal failure, intracerebral hematoma</td>
</tr>
<tr>
<td>Kobayashi et al., 1985 (6)</td>
<td>1 (40/M)</td>
<td>Headache, papilledema, deafness, right 5th, 6th CN palsies, ataxia</td>
<td>Tentorial thickening, enhancement (CT scan)</td>
<td>None/none</td>
<td>Thick tentorium with granulomas</td>
<td>Steroids, antibiotics</td>
<td>Progression</td>
<td>Chronic renal failure</td>
</tr>
<tr>
<td>Martin et al., 1989 (1)</td>
<td>2 (68/M)</td>
<td>Headache, papilledema, deafness, right 7th, 9th, 12th CN palsies</td>
<td>Tentorial thickening, enhancement (CT scan)</td>
<td>24/none</td>
<td>Fibrotic thickening of the dura, mild inflammatory infiltrate</td>
<td>Steroids</td>
<td>Headache relief</td>
<td>Acute pneumonia</td>
</tr>
<tr>
<td>Martin et al., 1990 (1)</td>
<td>3 (58/M)</td>
<td>Headache, left 7th, bilateral 8th, and right 10th and 11th CN palsies, ataxia</td>
<td>Tentorial thickening (MRI/CT scan)</td>
<td>51/none</td>
<td>Thick dura with chronic inflammatory infiltrate</td>
<td>Steroids, azathioprine, radiation</td>
<td>Stabilization</td>
<td>None</td>
</tr>
<tr>
<td>Willing &amp; Broghamer, 1992 (4)</td>
<td>4 (35/F)</td>
<td>Headache, 6th CN palsy</td>
<td>Enhancing mass in the sella/cavernous sinuses (MRI)</td>
<td>45/none</td>
<td>Dense collagen with scant inflammation</td>
<td>Steroids</td>
<td>Resolution of 6th CN palsy</td>
<td>None</td>
</tr>
<tr>
<td>Hamilton, Smith, and Lessell, 1993</td>
<td>5 (65/F)</td>
<td>Headache, bilateral 6th CN palsies</td>
<td>Diffuse dural thickening, enhancement (MRI)</td>
<td>85/negative</td>
<td>Thick dura with chronic inflammatory infiltrate</td>
<td>Steroids, azathioprine</td>
<td>Stabilization</td>
<td>Chronic cholecystitis</td>
</tr>
<tr>
<td>(6/F)</td>
<td>Bilateral optic neuropathy</td>
<td>Frontal dural thickening, enhancement (MRI)</td>
<td>95/positive</td>
<td>Thick dura with chronic inflammatory infiltrate</td>
<td>Steroids, azathioprine, radiation</td>
<td>Stabilization</td>
<td>Temporal arteritis</td>
<td></td>
</tr>
<tr>
<td>3 (33/M)</td>
<td>Headache, bilateral 6th CN palsies, orbital pain</td>
<td>Basilar dural thickening, enhancement (MRI)</td>
<td>27/none</td>
<td>Thick dura with chronic inflammatory infiltrate</td>
<td>Steroids, chloroquine, radiation</td>
<td>Stabilization</td>
<td>Hypopituitarism</td>
<td></td>
</tr>
</tbody>
</table>

CN. cranial nerve.

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origin. Moore et al. (9) published another case in 1985, attributed to syphilis with similar pathology and a late positive serum fluorescein treponemal antibody titer. A case of biopsy-confirmed tuberculous cranial pachymeningitis was reported by Callebaut et al. (10) with evidence of resolution by MR imaging with Gd-DTPA after antituberculous therapy. Gorell et al. (11) utilized positive fungal stains and fluorescent antibody titers of the involved dura to link another case to systemic candidiasis.

Neurosarcoidosis is a potential noninfectious cause of dural thickening and enhancement on imaging studies. CT has revealed contrast-enhancing densities involving the falx, tentorium, and leptomeninges in patients with sarcoidosis (12,13). A more extensive review (14) of 21 patients with neurosarcoidosis studied with CT and MR imaging concluded that MR scanning is the best means of detecting parenchymal lesions, whereas CT is useful for detecting diffuse meningeal involvement. None of the MR scans in that study were performed with Gd-DTPA, and Phillips et al. (15) have subsequently stated that MR imaging with Gd-DTPA is the optimal means of detecting meningeal lesions, although it is nonspecific for inflammatory versus neoplastic etiology. Khaw et al. (16) reported two cases of neurosarcoidosis with enhancement of the tentorium cerebelli or meninges with Gd-DTPA-enhanced MR imaging. No intracranial dural biopsies were obtained, and the diagnoses were based upon other clinical signs compatible with sarcoidosis.

Rheumatoid arthritis has also been associated with cranial pachymeningitis, in addition to its more common involvement of the cervical spine. Bathon et al. (17) described a patient with rheumatoid arthritis who developed headaches and an optic neuropathy. A brain CT demonstrated diffuse tentorial enhancement and involvement of the optic chiasm. Biopsy revealed fibrosis of the dura with a chronic inflammatory infiltrate without giant cells or rheumatoid nodules. Weinstein et al. (18) had presented a similar patient with rheumatoid arthritis who had a junctional scotoma from a chiasmal neuropathy with very similar CT and biopsy findings. Yuh et al. (19) reported another rheumatoid arthritis patient with headache, diffuse meningeal enhancement with Gd-DTPA-enhanced MR imaging, and similar dural pathology on biopsy.

Intracranial hypertrophic pachymeningitis has been reported in a single case of multifocal fibrosclerosis (20). This rare disorder is characterized by clinical findings that may include mediastinal fibrosis, retroperitoneal fibrosis, orbital pseudotumor, Reidel's thyroiditis, and sclerosing cholangitis. The patient presented was a 34-year-old man with episcleritis, orbital pseudotumor, and sclerosing cholangitis with tentorial thickening on MR imaging. Intracranial biopsy revealed chronic inflammatory cells in a fibrotic dura.

Rarely, cases of orbital pseudotumor have been described with intracranial extension (21–23). Clifton et al. (2) recently retrospectively reviewed 90 cases of orbital pseudotumor, and found 8.8% had CT evidence of intracranial extension. Most of these cases had localized extension into the adjacent superior orbital fissure or ipsilateral cavernous sinus, but two patients had more extensive intracranial involvement. The pathology in these cases is identical to that seen in pachymeningitis, and an overlap of the two syndromes may be present in those cases with both orbital and intracranial dural involvement.

Given the difficulty in distinguishing idiopathic cases of cranial pachymeningitis from those secondary to other disease processes, such as syphilis, tuberculosis, rheumatoid arthritis, or sarcoidosis, extensive systemic evaluations are necessary in symptomatic patients with an elevated ESR and dural thickening on neuroimaging studies. An appropriate evaluation would include a general physical examination; a brain MR scan with Gd-DTPA; a chest radiograph; an ACE level, rheumatoid factor, and FTA-ABS; CSF examination; and a dural biopsy. So few cases have been reported that it is difficult to offer guidelines for treatment. At present it would seem most appropriate to initiate therapy with prednisone in the range of 40–80 mg/day. Another immunosuppressive drug such as azathioprine could subsequently be introduced if desired to achieve tapering off prednisone and reduction of the risk of systemic side effects from chronic corticosteroid therapy.

REFERENCES


Spontaneous Rupture of an Intraorbital Hydatid Cyst
A Rare Cause of Acute Visual Loss

M. Memet Özek, M.D., M. Necmettin Pamir, M.D., and Aydin Sav, M.D.

A very rare cause of acute visual loss due to the spontaneous rupture of an intraorbital hydatid cyst is presented. Acute onset was thought to be due to volume expansion and inflammatory reaction of orbital structures to ruptured cyst fluid.

Key Words: Orbita—Echinococcosis—Hydatid cyst—Orbital hydatid—Proptosis—MRI.

Two species of Echinococcus may infect the human nervous system: E. granulosus and E. multilocularis (1,2). These two cestodes differ in life cycle, morphology, and epidemiology. Central nervous system infestation by E. granulosus, called hydatid cyst disease, usually occurs in the cerebrum, but may also occur in the spine (1,3). Only a few papers of orbital hydatid disease have been reported from different areas of the world where hydatid disease is prevalent (1,3–9). Orbital hydatid cyst disease is a very rare cause of proptosis and loss of visual acuity, even in densely endemic countries.

Although possible spontaneous rupture of a hydatid cyst is not mentioned in the literature very often (10), we present a case of a unilateral orbital hydatid cyst, in whom an acute loss of visual acuity occurred secondary to spontaneous primary cyst rupture.

CASE REPORT

A 52-year-old female was admitted to our hospital with a 6-month history of painless proptosis of the right eye and a 4-day history of sudden visual loss accompanied by severe orbital pain.

Neuro-ophthalmologic Examination

Right eye: Examination revealed total visual loss without light perception and optic atrophy. A proptosis of 28 mm with inferior and lateral globe displacement and limited motility in all directions of gaze was observed.

Left eye: Fundoscopic and visual field examination of her left eye was normal.

General physical examination and laboratory tests were unremarkable except for a positive Ca-
soni test. The Weinberg complement fixation test was normal. MRI showed multiple well-defined cysts occupying the superior aspect of the orbit, causing erosion of the orbital roof. The cyst signal was low intensity on T1-weighted images and high intensity on T2-weighted images (Fig. 1). No other focus of infiltration was uncovered.

Surgical Procedure

The preoperative diagnosis was orbital hydatid cyst. A right Kronlein-Berke approach was used to explore the orbital cavity. After opening Tenon's capsule, the very edematous orbital contents protruded from the craniectomy site. There was a very thick irregular fibrous membrane that had a moderate number of adhesions to the orbital contents and seemed to be the remains of a former primary cyst. Within this thick ruptured capsule we found three large cysts. These daughter cysts were carefully removed without rupturing their very thin membranes. After the cysts were excised, the orbital cavity was irrigated with 3% NaCl. Mebendazole was initiated immediately following the operation.

Pathology

Serial sections were taken for histopathological examination from the surgically removed tissues of the orbit. Morphologically, there were four separate cysts, one of which had a very thick membrane with heavy lymphocyte infiltration, both suggesting chronicity. The remaining three cysts were multilayered structures, whose characteristics were consistent with classic hydatid cysts. It is unlikely these small-calibered cysts ("daughter" cysts) had no typical outermost layer consisting of fibrous tissue; however, they showed a relatively thick, laminated, and acellular outer membrane nucleated inner germinative membrane. But there were no accompanying brood capsules or scolies in the cyst fluid. Although the cyst fluid was centrifuged and examined repeatedly, no evidence of free hooklets or scolies was found. The theory of four particular cysts in the same vicinity might be formulated as the "mother" cyst which possibly gave birth to a couple of small-calibered "daughter" cysts, which really had no time to form a thick enwrapping fibrous capsule around them.

Follow-up

At 7 months following surgery, proptosis was decreased to 17 mm, ocular motility limitation was improved, and visual acuity of the right eye did not improve. There were no signs of recurrence on the follow-up MRI (Fig. 2).

DISCUSSION

Hydatid cyst, a lesion that appears during the evaluation of the parasite *Echinococcus granulosus* in man as an accidental host, can be found in various sites in the human body. Despite the fact that the CNS is affected in about 2% of all cases of hydatid

FIG. 1. There are three hydatid cysts within the orbital cavity. Notice the severe proptosis.
disease, there are limited reports of CNS infestation in the literature (1-10). Orbital hydatidosis is an even more unusual manifestation of *E. granulosus* infestation. Although subretinal, vitreal and anterior chamber hydatid cysts have been reported occasionally, the orbit is the most common site of ophthalmologic involvement (4,11). The prognosis of orbital hydatidosis is strongly influenced by early diagnosis on a relatively high index of suspicion of hydatidosis, and proper surgical treatment.

In all reported cases, the chief complaint was a slowly progressive unilateral proptosis. Morales and colleagues (4) described the duration of symptoms before consultation as being from 3 months to 2 years. But in our case, total visual loss and severe orbital pain occurred in 1 day, and was thought to be due to a sudden volume expansion secondary to the cyst rupture and inflammatory reaction of the orbital content with the cyst fluid. Our surgical findings supported also this and made our case unique.

The computed tomography (CT) appearance of orbital hydatid cyst is well defined (5,6). When examining a lesion on CT suggesting hydatid cyst, the differential diagnosis should always include chronic hematic cyst, abscess, dermoid and epidermoid cysts, and teratomas. Since these entities, along with hydatid cyst, typically produce a similar low-density image on CT, CT is not very helpful in diagnosing a hydatid disease in the orbit. However, the magnetic resonance image (MRI) appearance of a lesion with high intensity on T2 and low intensity on T1 helps to rule out other cystic lesions with less water content. In our opinion, MRI should follow CT for all intraorbital cystic lesions to avoid misdiagnosis and serious consequences, such as cyst rupture, with resultant anaphylactic reaction or local spread.

A lateral approach into the orbital cavity will prevent the risk of intracranial seeding and is therefore recommended. We strongly believe that a transcranial orbital approach is contraindicated in orbital hydatid disease because of the potential danger of cranial seeding. In case of spontaneous or accidental cyst rupture during surgery, corticosteroids are recommended to avoid the ensuing inflammatory reaction.

Sudden visual loss due to the spontaneous rupture may accompany orbital hydatid cyst disease. Therefore, all intraorbital hydatid cysts should be decompressed by a lateral orbitotomy immediately.

REFERENCES

Miller Fisher Syndrome Mimicking Stroke in Immunosuppressed Patient with Rheumatoid Arthritis Responding to Plasma Exchange

Lawrence M. Cher, M.B.B.S., B.Sc (Med) and John M. Merory, M.B.B.S., F.R.A.C.P.

A patient with rheumatoid arthritis on immunosuppressive therapy was admitted to hospital with the sudden onset of diplopia and ataxia. Because of the history, a stroke was thought most likely. However, as he progressed a diagnosis of the Miller Fisher syndrome was established. He responded to plasma exchange. This presentation is highly unusual and has not previously been described. In addition, the possibility of immune dysregulation setting the stage for the development of this syndrome is discussed. The role of plasma exchange for this condition is also reviewed.

Key Words: Miller Fisher syndrome—Rheumatoid arthritis—Stroke—Immuno-dysregulation—Plasma exchange.

The Miller Fisher Syndrome (1) is well known and is usually regarded as a variant of the acute inflammatory demyelinating polyradiculoneuropathies or Guillain-Barré syndrome (2–4), although there have been dissenting opinions (5,6). We are unaware of any reports of this syndrome beginning paroxysmally, mimicking a vascular event. The occurrence of Miller Fisher syndrome in a patient with rheumatoid arthritis on immunosuppressive therapy may have been a random event. Consideration is given to a possible relationship between these two disorders.

CASE REPORT

The patient was a 66-year-old male with a 5-year history of rheumatoid arthritis. He previously had symmetrical polyarthritis, rheumatoid nodules, and interstitial lung disease. His disease was stable and controlled with low-dose prednisolone (5 mg), methotrexate (10 mg weekly), and hydroxychloroquine (400 mg bid).

At 3 weeks prior to admission he developed a flu-like illness with pharyngitis, myalgias, and lethargy, and 5 days prior to admission he suddenly developed horizontal diplopia and frontal headache while driving. On leaving the car his gait was unsteady. This continued for the following 4 days and was accompanied by vertigo, tinnitus, and subjective hearing impairment. He was admitted to hospital.

Examination demonstrated dilated but equal pupils, which reacted sluggishly to light. Horizontal gaze-evoked nystagmus was more prominent in the abducting eye in either direction (dissociated nystagmus). Adducting saccades were normal and therefore not typical of internuclear ophthalmople-
No other cranial nerve abnormality was detected. Tone and power were normal, but a moderately severe truncal ataxia was demonstrated. Deep tendon reflexes were absent. Sensory testing revealed loss of vibration in the lower limbs and trunk to the lower thorax. Cerebral computed tomography (CT) scans with fine cuts through the posterior fossa was normal as was a Tension test. Erythrocyte sedimentation rate (ESR) was 25 mm/h.

Over the next 2 days, he progressively developed external ophthalmoplegia, moderate bilateral ptosis, and facial diplegia, and very diminished pupillary light reflexes. Horizontal eye movements were restricted to 20 degrees rightward and 30 degrees leftward. Upgaze was limited to 15 degrees and downgaze to 10 degrees. Nerve conduction studies were normal except for prolonged F waves suggesting proximal nerve involvement. Cerebrospinal fluid (CSF) analysis showed normal glucose, and protein of 0.46 g/L with no cells. Viral cultures of CSF were normal. A diagnosis of Miller Fisher syndrome was made.

Because his condition was progressive he was treated with plasma exchange (3 L/day for 5 days). This was complicated by mild hypotension. Whereas previously his clinical state had worsened, with commencement of treatment no further deterioration occurred. By day 4 of plasma exchange, he started to improve and this continued such that his gait became normal, and ptosis resolved. The diplopia persisted as did the areflexia. Over the next 5 weeks, his tendon reflexes and pupillary light reflexes returned and his ophthalmoplegia resolved.

**DISCUSSION**

We are unaware of any reported cases of Miller Fisher syndrome that have begun paroxysmally as with our patient. The importance of the history in establishing the diagnosis in neurological problems is always stressed. However, in this case the dear history of sudden onset caused diagnostic confusion and delay in definitive therapy. The sudden onset of diplopia and unsteady gait and vertigo, associated with nystagmus and truncal ataxia is usually due to a vascular event. The “dissociation” between history and signs was perplexing initially until the development of external and internal ophthalmoplegia completed the clinical picture of areflexia, ataxia, and absent vibration sense. Although acute inflammatory demyelinating polyradiculoneuropathies can have a rapidly progressive course, patients do not describe such abrupt commencement of symptoms. One possible mechanism to explain the sudden onset of symptoms is the sudden decompensation of progressive oculomotor weakness. However, this does not explain the simultaneous onset of ataxia.

The association with rheumatoid arthritis may be more than fortuitous. Neuropathy in patients with rheumatoid arthritis has been well documented (7) but the etiology has been unclear. The literature contains anecdotal reports of the association between rheumatoid arthritis and acute inflammatory demyelinating polyradiculoneuropathy and chronic inflammatory demyelinating polyneuropathy. In a review of 66 consecutive patients with acute and chronic inflammatory demyelinating polyneuropathy seen at one hospital, 15% had associated autoimmune disorders, including one with rheumatoid arthritis and acute inflammatory demyelinating polyneuropathy (8). The occurrence of Miller Fisher syndrome in a patient with rheumatoid arthritis has been documented (9). This was attributed to concomitant gold therapy, as gold has been associated with acute inflammatory demyelinating polyneuropathy (10). However, rheumatoid arthritis may have been the underlying factor.

It has been suggested (11–13) that immunosuppression may play a role in the pathogenesis of acute inflammatory demyelinating polyneuropathy. Interestingly, the patient described by Monteiro and colleagues (12) developed Miller Fisher syndrome following 5 weeks of prednisone therapy for angioimmunoblastic lymphadenopathy, a condition with both autoimmune and immunodeficient features. They postulated that the immunologic deficiency may be crucial to the development of acute inflammatory demyelinating polyneuropathy by impairing T-suppressor cell function leading to immune dysregulation. The three patients described by Lisak and coworkers (11) with inflammatory demyelinating polyneuropathy and Hodgkin's disease all showed evidence of impaired cell-mediated immunity (CMI) (11). They refer to the occurrence of acute inflammatory demyelinating polyneuropathy in patients with variable degrees of immunosuppression, such as systemic lupus erythematosus, pregnancy, and after cytomegalovirus (CMV) or Epstein-Barr virus (EBV) infections. They suggest that selective depression of CMI from whatever cause could perturb those aspects of the immune system which prevent self-directed immune events. The occurrence of acute inflammatory demyelinating in a renal transplant patient (13) on prednisone and azathioprine furnishes further evidence that immunosuppression does not
The role of plasma exchange in Miller Fisher syndrome has not been systematically assessed. To our knowledge only one individual case report has been published (16), and a passing reference is made in another (17). This therapy has proven to be of benefit in acute inflammatory demyelinating polyneuropathy (18). In a review of cases of acute inflammatory demyelinating polyneuropathy at Royal Prince Alfred Hospital (Sydney, Australia) Pollard mentioned six patients with Miller Fisher syndrome, five of whom were treated with plasma exchange because of severe ataxia. All responded clinically (unpublished data).

Although the length of time to recovery in Miller Fisher syndrome is variable, in most case reports the average time course to recovery was approximately 3 to 4 months. Reviewing 10 cases from various reports in which it was possible to estimate the time to recovery from symptoms and signs, the average length of duration was 6.7 months with a mean of 5 months. Sauro and coworkers (19) reported 10 patients who were asymptomatic within 1 to 3 months. Although Miller Fisher syndrome is usually thought to be a benign condition cases have been reported who progressed to intubation and ventilation (20). Our patient was clearly progressing and plasma exchange led to stabilisation initially and then improvement to normal over 5 weeks. While too much weight should not be given to single case reports of plasma exchange in acute inflammatory demyelinating polyneuropathy, it is unlikely that a large enough series of patients with Miller Fisher syndrome could be gathered to perform a controlled trial. Most neurologists would treat Miller Fisher syndrome with plasma exchange. As this modality of therapy is most effective when commenced early, the delay in diagnosis of patients such as ours could be important.

REFERENCES

Optic Neuritis Associated with Familial Mediterranean Fever

A. Lossos, M.D., S. Eliashiv, M.D., E. Ben-Chetrit, M.D., and A. Reches, M.D.

Familial Mediterranean fever (FMF) is an inherited disorder characterized by recurrent attacks of fever and polyserositis of unknown origin. Neuro-ophthalmologic involvement is rare. We describe a previously unreported association of FMF with optic neuritis in two patients.

Key Words: Optic neuritis—Periodic disease—Familial Mediterranean fever.

Familial Mediterranean fever (FMF), also known as periodic disease or recurrent polyserositis, is an autosomal recessive disorder primarily affecting individuals of non-Ashkenazi Jewish, Armenian, Turkish, and Arab families (1). The disease usually begins with fever followed by a self-limited episode of peritonitis, pleuritis, or synovitis. Less common manifestations include skin rash, myalgia, and splenomegaly, and some patients may develop systemic amyloidosis leading to chronic renal failure. Initial attacks appear in childhood or adolescence and recur at irregular intervals thereafter. Diagnosis of FMF is based on the clinical presentation and family history, since no pathognomonic laboratory test exists (1). Treatment with colchicine has been shown to reduce the attack rate and to prevent renal amyloidosis (2).

Neurologic involvement in FMF has been rarely documented (1). We describe two patients with FMF who developed optic neuritis.

CASE REPORTS

Patient 1

A 24-year-old woman of Jewish-Moroccan extraction has been evaluated for painless left monocular visual loss, which developed over a few days. She had a 10-year history of FMF manifested by recurrent attacks of abdominal pain and paroxysmal right shoulder arthritis, treated sporadically with colchicine 0.5 mg/day. Her family history was negative for any neurological disease and she denied smoking, alcohol, or drug abuse. On examination, her left eye visual acuity was reduced to 20/200, and a left relative afferent pupillary defect was identified. No optic disk pallor was present on ophtalmoscopy. Visual fields examination disclosed a left paracentral scotoma. The rest of her general and neurological examination was normal.
Routine blood evaluation was normal including erythrocyte sedimentation rate, acute phase reagents, serological tests for syphilis, Rose-Waaler and latex agglutination, antinuclear antibodies, and whole-blood vitamin B<sub>12</sub> levels. Results of chest radiographs and lumbar puncture were normal, including the absence of oligoclonal cerebrospinal fluid bands. Visual evoked potentials (VEP) were significantly prolonged over the left eye. Brainstem auditory evoked potentials (BAEP) and magnetic resonance imaging (MRI) of the brain were normal. A retrobulbar neuritis was diagnosed, and a course of oral prednisone 60 mg daily was started, tapered down over a 2-week period. Colchicine 0.5 mg b.i.d. was reintroduced. The patient’s visual acuity returned to normal, and her neurological follow-up has been unremarkable during the last 2 years.

Patient 2

A 28-year-old man of Jewish-Kurdish extraction with an 8-year history of FMF treated with colchicine 0.5 mg t.i.d., was evaluated for a subacute right monocular blurring of vision that occurred 1 week following an attack of fever and abdominal pain. His right eye visual acuity was reduced to 20/40 with a decreased red color perception and an abnormal light brightness comparison test. Visual fields examination disclosed a right central scotoma, but no optic disk pallor was identified. The rest of his general and neurological examination was normal. Laboratory evaluation similar to the 1st patient was unremarkable. Right eye visual evoked potentials were prolonged. Brainstem auditory evoked potentials and brain CT were normal. The patient improved spontaneously over a few months with resolution of visual field defect, save a decrease in red color perception. No neurological abnormalities recurred over a 3-year follow-up. As in the first patient, no cases of optic neuritis were reported in his family.

DISCUSSION

Various ocular manifestations have been described in FMF, including colloidlike bodies, episcleritis, uveitis, and retinal detachment (1,3). Neurologic involvement is rare and consists of headaches, nonspecific electroencephalographic changes during attacks, and recurrent aseptic meningitis (1,4). An association with Mollaret’s meningitis has been also documented (5). Since optic neuritis has not been previously reported with FMF, and, however coincidental this association may be, it deserves some comments.

FMF gene has been recently mapped to the short arm of chromosome 16 (6); however, it has not been yet cloned and its exact product is still unknown. Influx of polymorphonuclear leukocytes into the affected tissues during an attack, acute phase reactants overproduction and cutaneous vasculitis have implicated the immune system in the pathogenesis of FMF (7). In addition, relative bone marrow plasmacytosis, T-cell function abnormalities, circulating immune complexes and lymphocytotoxins have been described (7). Optic neuritis is associated with various immune-mediated disorders, such as Behçet’s disease (8), Sjogren’s syndrome (9), systemic lupus erythematosus, and nonspecific autoimmune abnormalities (10). This may suggest a possible link to FMF. The proximity of optic nerve involvement to a febrile attack in our second patient may either suggest a common basic disease process or represent Uhthoff’s phenomenon.

Colchicine has been reported to cause keratitis, peripheral neuropathy, and vacuolar myopathy (11). It may be also indirectly involved in neurological complications through an induction of vitamin B<sub>12</sub> deficiency (12). However, no association with optic neuritis has been reported. Our patients had normal levels of whole-blood vitamin B<sub>12</sub> and did not use any other drugs.

Isolated optic neuritis may precede the development of clinically definite multiple sclerosis up to 15 years (13), and we cannot rule out this possibility, since our follow-up period is only about 3 years. Nevertheless, the lack of oligoclonal CSF bands and of additional clinical and paraclinical evidence (i.e., normal MRI in one patient and brainstem auditory evoked potentials in both) of disseminating neurological involvement does not support this diagnosis (14).

REFERENCES

The 1991 Japanese Neuro-ophthalmology Society Meeting

Masato Wakakura, M.D., D.Sc.

At the 29th meeting of the Japanese Neuro-ophthalmology Society, held in Kagoshima (organizer, Professor Norio Ohba) on November 7-8, 1991, 125 papers were presented. This article discusses several papers of particular interest.

OPTIC PATHWAY

Professor Mitsuhiro Osame (Kagoshima) presented an overview on HTLV-I-associated myelopathy (HAM). According to a nationwide survey of HAM in Japan, there were 710 patients with HAM (1), and approximately 1,150 patients throughout the world. Ocular complications include anterior uveitis, retinal vasculitis, cotton-wool spots, pigmentary retinal degeneration, and keratoconjunctivitis sicca. Sekine and colleagues (Sapporo) reported unilateral macular degeneration and disc edema associated with HAM. Arimura and colleagues (Kagoshima) observed abnormal smooth pursuit movements in 12 of 26 HAM patients, which appeared to be related to the severity of myelopathy, possibly due to the involvement of the optic pathway by leukoariosis usually present in brain white matter of these patients on magnetic resonance imaging (MRI).

A retinal cause is usually suggested for visual disturbance in the multiple evanescent white-dot syndrome (MEWDS). Ozaki and colleagues (Miyazaki) reported two cases with MEWDS, both showing unilateral enlargement of the blind spot, reduced ratio of the light peak/dark trough of EOG, and subnormal ERG. However, in one of the cases, there were unilateral visual loss, relative afferent pupillary defects, and reduced critical fusion flicker frequency. Optic neuropathy was thus suspected. These findings support those of Dodwell and colleagues (2).

An 83-year-old man, who has lived alone for the past 30 years, noted bilateral visual loss. Corrected visual acuity of 0.2 OD and 0.5 OS could not be explained by his condition of mild cataracts. Low blood level of the vitamin B group was found. Visual recovery was followed relatively quickly by regular intake of food and vitamin B treatment. Such patients with mild deficiency optic neuropathy have recently been found to be rather prevalent in Japan. (Taguchi and colleagues, Hiroshima).

Studies for evaluating visual function in optic neuritis were reported. P-100 latency in pattern-visual evoked potentials show slower recovery than visual acuity or latency of light response (Chin and colleagues, Sapporo). Temporal modulation transfer function is recovered more slowly than visual acuity or Humphrey perimetry (Abe and colleagues, Niigata). Woung and colleagues (Sagamihara) found central critical flicker frequency to be a sensitive means for detecting subtle abnormality at the recovery stage or in the fellow eye for cases of unilateral visual loss.

Prostatic cancer metastasizes approximately 2% to 4% to the brain, and prognosis is quite poor. A 62-year-old man, who had compression optic neuropathy due to metastasized prostatic cancer at the suprachiasmal region, was treated with progesterone and then Estracite (estrogen + nitrogen mustard). Dramatic recovery from the original cancer, metastasized cancer, and optic neuropathy was achieved (Morikawa and colleagues, Osaka).

Acquired cerebral dyschromatopsia was discussed by three speakers (Yoshizawa and colleagues, Niigata; Takano and colleagues, Tokyo; Yokoyama and colleagues, Akita). Their clinical findings
showed some variation, this depending partly on the particular tests used. There still appears to be no adequate examination for detecting cerebral dyschromatopsia.

**OCULAR MOTOR SYSTEM**

Miniature eye movement was studied, using a fundus haploscope with a half-mirror (Sato, Shiga). The half-mirror is positioned such a way as to visualize the subject's fundus image on a television monitor. When the fundus image was completely synchronized with eye movement, the stabilized retinal image could not be seen by the subject. Under this condition, there was only slight drift movement. The hypothesis that the physiological role of the miniature movement is to maintain fixation was confirmed.

Takano and colleagues (Sagamihara) presented four cases with carotid-cavernous fistula (CCF) who had ocular motor abnormality but neither chemosis nor proptosis. By superselective angiography, atypical CCF was shown to drain into cortical veins rather than into ophthalmic veins. Such cases may be difficult to diagnose initially as CCF, and there is great risk of brain hemorrhage.

Oku and colleagues (Osaka) reviewed 19 cases of diabetic ophthalmoplegia and found 14 cases of abducens palsy to have better control on HbA1C than 3 cases with oculomotor palsy. Spontaneous recovery was seen in all cases at 95 days on average. It was considered that surgery should not be conducted until at least 3 months had passed from the onset.

Four cases with alternating skew deviation (ASD) or bilateral adducting hypotropia were presented by Kiyosawa and colleagues (Sendai). Three cases were pinealoma and another was postviral encephalitis. In all cases, ASD was followed by unilateral skew deviation. The authors suggest ASD to be a transient phenomenon appearing when midline lesion at the midbrain is symmetrically stimulated.

**MISCELLANEOUS**

Development of the human ciliary muscle was studied immunohistochemically by Tanino and colleagues (Tokyo). Ciliary muscle cells were identified in specimens at the 12th gestational week and actin-positive cells were observed initially in the posterior half of the ciliary body at 17th gestational week. Development of the anterior half of the ciliary muscle is apparently delayed.

Image analysis of pupillary movement by computer was reported by Fujita and colleagues (Sagamihara). Six cases with tonic pupil were analyzed and all showed segmental palsy of the pupil. Nasal side was more dilated in five cases than the temporal side and light response was significantly reduced on the nasal side in three cases. The oculomotor nerve to the iris may be differently innervated for the temporal and nasal sides, and damage to the nasal side may occur earlier.

**LEBER'S HEREDITARY OPTIC NEUROPATHY**

Eight papers were presented in a minisymposium entitled “Mitochondrial Mutations and Neuro-ophthalmology.” The main topic was genetic analysis in Leber's hereditary optic neuropathy. Dr. J. Imachi who has studied very large series of this disease (3) organized this symposium. The extraordinary development in this field has demonstrated the need to clarify several problems, such as why there are more female cases in Japan than in Europe and the United States, possible factors that initiate optic neuropathy in cases with...
mitochondrial mutation, the research for spontaneous recovery, and the availability of drugs effective for recovery. The significance of heteroplasmy is also of interest in regard to this disease, but in reported cases in Japan, heteroplasmy apparently is not related to severity or onset. It is expected that this disease will be studied further throughout the world because of the limited number of cases and the racial differences.

REFERENCES

Editorial Comment

Of the 19 patients with diabetic ophthalmoplegia mentioned in the report by Oku and colleagues, all were seen to recover spontaneously by 95 days on the average. The statement that "surgery should not be conducted until at least 3 months had passed from the onset" seems inappropriate in this context. Diabetic ophthalmoplegia characteristically clears within 90 days and, of course, these patients do not need surgery. Other causes of cranial neuropathy can occur, obviously, in diabetics and those must be carefully differentiated by appropriate investigations.

J. L. Smith, M.D.
Editor
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Literature Abstracts


The authors report their experience using the Hess screen on patients with myasthenia gravis during a Tensilon test. They defined a positive test as a 50% or greater reduction in the initial strabismic deviation within 1 minute of Tensilon infusion. They tested 10 normals, 12 nonmyasthenic patients with acquired strabismus, and 10 patients with strabismus from ocular myasthenia gravis. None of the nonmyasthenic or control patients had a positive test, and all myasthenic patients had 50% or greater reduction in their deviation. They feel that the Hess screen used with Tensilon is a sensitive and specific test for the diagnosis of strabismus caused by myasthenia gravis.

Lyn A. Sedwick, M.D.


A 15-year-old boy is described who has a 2-week history of alternating anisocoria with the pupils reversing in size 2 to 4 times daily. His workup included a full neurologic examination and magnetic resonance scanning of the head, both of which were normal. It is unclear what caused this young man’s alternating anisocoria.

Lyn A. Sedwick, M.D.


Dr. Burde gives a nice “clinical capsule” of neuro-ophthalmic problems related to diabetes. Entities such as optic disc hypoplasia in children of diabetic mothers, diabetic cranial mononeuropathy involving ocular motor nerves, diabetic papillopathy, and zygomycosis are discussed among others. A very nice list of references is included in this succinct “perspective” article.

Lyn A. Sedwick, M.D.


The author reports his experience with 6 patients who had a “V” esotropia and excyclotropia after surgery for bilateral superior oblique palsy. These patients were successfully treated with recession of the inferior recti muscles bilaterally.

Lyn A. Sedwick, M.D.


An interesting point-counterpoint discussion of the merit of using high-dose intravenous corticosteroids to treat central retinal artery occlusion in temporal arteritis.

Lyn A. Sedwick, M.D.
Malignant Lymphoma of the Ocular Adnexa Associated with the Benign Lymphoepithelial Lesion of the Parotid Glands. Report of Two Cases.
Font RL, Laucirica R, Rosenbaum PS, Patrinely JR, Boniuk M. *Ophthalmology* 1992;99:1582-7 (Oct). [Reprint requests to Dr. R. L. Font, Ophthalmic Pathology Laboratory, Cullen Eye Institute, Baylor College of Medicine, Houston, TX 77030.]

Two patients with malignant orbital lymphoma and related benign lesions involving parotid glands are discussed. Neither had Sjogren syndrome and the authors believe theirs is the first report of “malignant lymphoma of the ocular adnexa occurring in patients with a benign lymphoepithelial lesion of the parotid glands.”

*Lyn A. Sedwick, M.D.*

Orbital Lymphangioma. Correlation of Magnetic Resonance Images and Intraoperative Findings.

The authors extensively report their experience with magnetic resonance imaging in the management of 12 patients with orbital lymphangiomas.

*Lyn A. Sedwick, M.D.*


A 15-month-old boy had excision of an orbital tumor which proved to be a malignant peripheral nerve sheath tumor. He was followed without further intervention for 9 years and had no evidence of recurrent tumor. The authors argue for conservative management in such cases if the initial tumor is thought to be completely excised.

*Lyn A. Sedwick, M.D.*

A New Classification of Superior Oblique Palsy Based on Congenital Variations in the Tendon.

The authors note that often (87%) a structural abnormality of the superior oblique tendon is present at surgery in patients with congenital palsy, whereas such abnormalities are rare (8%) in acquired palsies. They define several different types of anomalous tendons based on their surgical observations and suggest that surgery may need to be custom-tailored to whatever specific tendon anomaly may be found.

*Lyn A. Sedwick, M.D.*

Multiple Cranial Neuropathies: Presenting Signs of Systemic Lymphoma.

A patient is described who four years after liver transplantation presented with multiple ocular motor nerve palsies, right and left-sided, and an upper extremity motor neuropathy. Lumbar puncture ×2, neuroimaging, and total body computed tomography failed to disclose an underlying disorder; however, sural nerve biopsy showed endoneurial perivasculare infiltration with lymphoid cells consistent with Burkitt’s-type lymphoma. This case demonstrates the lengths to which one may need to go to diagnose systemic lymphoma with neural infiltration in a patient who is immunosuppressed and presents with cranial neuropathy.

*Lyn A. Sedwick, M.D.*

Disc Swelling: A Tall Tail?

The authors discuss a patient who presented with moderate visual loss and optic atrophy, right
eye, but elevation of the left optic disc. Computed tomography and magnetic resonance scans of the head were unremarkable. Lumbar puncture did reveal elevated cerebral spinal fluid pressure but also an abnormal protein. Approximately a year later, because of lower extremity difficulties, investigation led to diagnosis of a spinal cord tumor (malignant ependymoma). The authors discuss this very interesting presentation of visual loss and disc edema in a patient with a spinal cord tumor.

Lyn A. Sedwick, M.D.

Multifocal Choroiditis and Choroidal Neovascularization Associated with the Multiple Evanescent White Dot and Acute Idiopathic Blind Spot Enlargement Syndrome. Callanan D, Gass JDM. Ophthalmology 1992;99:1678-85 (Nov). [Correspondence to Dr. J. D. M. Gass, Bascom Palmer Eye Institute, P.O. Box 016880, Miami, FL 33101.]

Seven patients who presented with or developed chorioretinal scars or neovascularization such as that seen with multifocal choroiditis or pseudo-presumed ocular histoplasmosis syndrome are discussed. All seven had photopsia and blind spot enlargement during their illness, and four had multiple evanescent white dot syndrome. The authors believe this to be yet another clinical disorder related to, or a subset of, acute idiopathic blind spot enlargement syndrome and multiple evanescent white dot syndrome.

Lyn A. Sedwick, M.D.


A very interesting volley of letter to editor and reply regarding a previously published report, which alleged that optic nerve decompression reverses visual defects in pseudotumor cerebri even in cases with functioning lumbo-peritoneal shunts but progressive visual loss. Dr. Wall correctly notes that continuously normal shunt function was not proven by the authors and that intermittent shunt dysfunction was possible. The authors concede this point but note that these patients had "clinically" functioning shunts and rather than revise them, in the face of normal cerebral spinal fluid pressure on routine testing, optic nerve sheath decompression offers an attractive, practical alternative if visual loss continues.

Lyn A. Sedwick, M.D.


The authors present 13 magnetic resonance-studied cases of optic nerve sheath meningioma and contrast the ability of magnetic resonance versus computed tomography to detect and define lesions. Clinical and magnetic resonance findings in 13 patients are summarized in a table and nice magnetic resonance pictures are included.

Lyn A. Sedwick, M.D.


The authors elaborate on a new system they developed for scoring field of single binocular vision. Their target is a (+), which permits the patient to appreciate torsional as well as horizontal diplopia. Their system seems to give a more accurate representation of disabling ocular misalignment than does the standard system.

Lyn A. Sedwick, M.D.


From the Mayo Clinic records, 160 cases of acquired ocular motor cranial nerve palsies from 1966...

The authors located 30 patients who had profound cortical visual impairment occurring between 6 and 12 months of age from a variety of causes. Half of these infants developed object vision. A history of birth asphyxia or postnatal hypoxia was associated with a poor prognosis for development of object vision. Radiographic studies that were done (mostly computed tomography) were not predictive for whether or not object vision would develop, although the authors postulate that more uniformly obtained magnetic resonance scanning might have added more predictive information.


A 21-year-old man treated 3 years previously for Hodgkin’s disease presented with visual loss left eye and a swollen optic disc. Magnetic resonance imaging showed diffuse enlargement of the left optic nerve. Lumbar puncture was not diagnostic, but radiation therapy administered to the left orbit, combined with intravenous and oral corticosteroid, resulted in marked improvement in vision and reduction in disc edema. Lymph node biopsy subsequently demonstrated recurrent lymphoma. The authors believe their patient had optic neuropathy as an initial symptom/sign of recurrent Hodgkin’s disease, which has not previously been reported.

Lyn A. Sedwick, M.D.


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A 73-year-old man had a rapidly progressive course of multiple strokes involving visual cortex bilaterally. Temporal artery biopsy was negative. Autopsy demonstrated a pulmonary adenocarcinoma and nonbacterial thrombotic endocarditis. Although this patient apparently did not have echocardiography, Dr. Rush points out that “conventional echocardiography” may miss these small, fibrin-platelet excrescences on heart valves, which may be a remote effect of carcinoma, but their presence should be diligently sought in any patient with embolic stroke.

Lyn A. Sedwick, M.D.


An 84-year-old with disseminated lymphoma presented 1 month after a normal routine eye examination with left proptosis and no light perception vision left eye. An orbital mass was found to be small-cell malignant lymphoma on fine-needle aspiration. Orbital radiation therapy was started 51 days after documentation of his visual loss, and his vision ultimately improved to 20/40 in this eye. A truly remarkable result!

Lyn A. Sedwick, M.D.
Superior Segmental Optic Hypoplasia in Identical Twins

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Key Words: Superior segmental optic nerve hypoplasia—Monozygotic twins—Diabetes mellitus.

We describe superior segmental optic hypoplasia in two 15-year-old male monozygotic twins. The mother had a 25-year history of Type I diabetes at the time of pregnancy. Both twins were healthy and developmentally normal. An older sister had unilateral superior segmental optic hypoplasia.

Corrected visual acuity was 20/30 in both twins. Twin 1 had superior segmental hypoplasia of the right optic disc (Fig. 1A). The nasal aspect of the left optic disc appeared segmentally hypoplastic (Fig. 1B). Humphrey 60-2 visual field testing in the right eye showed an inferior nonaltitudinal defect with mild superior constriction (Fig. 1C). The left visual field showed severe peripheral constriction with a small central island of preserved vision (Fig. 1D). In twin 2, both optic discs showed superior segmental hypoplasia (Fig. 2A,B). Visual field abnormalities in the right eye were virtually identical to those in the right eye of twin 1 (Fig. 2C). The left visual field showed diffuse peripheral constriction which was worse inferiorly (Fig. 2D).

COMMENT

Superior segmental optic nerve hypoplasia was first recognized as a distinct clinical entity by Petersen and Walton (1) in 1977. They described 17 children of diabetic mothers who had segmental optic nerve hypoplasia, good visual acuity, and inferior altitudinal or sector visual field defects. Subsequent cases of superior segmental optic hypoplasia have consistently involved offspring of insulin-dependent diabetic mothers (2,3).

Kim et al. (3) defined the ophthalmoscopic features of superior segmental optic nerve hypoplasia as consisting of (a) pallor of the superior disc; (b) relative superior entrance of the central retinal artery; (c) a superior peripapillary scleral halo; and (d) thinning of the superior peripapillary nerve fiber layer. They noted that the visual field defects in these patients were not typical of acquired optic nerve defects and questioned whether a regional...
impairment in retinal development could play a role in the pathogenesis.

Congenital malformations occur two to three times more commonly in infants whose mothers have insulin-dependent diabetes mellitus at conception (5). Considerable evidence exists that these malformations result from metabolic abnormalities early in the first trimester (5). As with any teratologic event, it is possible that affected individuals have an underlying genetic susceptibility.

Petersen and Holmes (4) found no cases of optic nerve hypoplasia in 28 children of diabetic mothers and concluded that, despite a high prevalence of maternal diabetes, superior segmental optic hypoplasia is a rare anomaly. As in our patients, superior segmental optic hypoplasia often occurs in patients without other systemic anomalies. The teratologic mechanism by which insulin-dependent maternal diabetes selectively interferes with the early gestational development of supe-
FIG. 2. Optic disc photographs and Humphrey 60-2 visual fields in twin 2. (A) Right optic disc photograph shows superior segmental optic hypoplasia. (B) Left optic disc showing mild superior segmental optic hypoplasia. (C) See right visual field shows an inferior nonaltitudinal defect that is virtually identical to the right visual field in twin 1. (D) Left visual field shows diffuse peripheral constriction that is worse inferiorly.

rior retinal ganglion cells or their axons is unknown.

REFERENCES


