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Message From the Editor

This issue marks the beginning of the third epoch of the Journal of Neuro-Ophthalmology. The journal began quarterly publication 23 years ago, in 1978, under the editorship of J. Lawton Smith, MD, as the Journal of Clinical Neuro-Ophthalmology. In 1994, the journal became the official publication of the North American Neuro-Ophthalmology Society (NANOS), shortened its name to the Journal of Neuro-Ophthalmology (JNO), and came under the editorship of Ronald M. Burde, MD. Through the years, JNO has become the most widely subscribed and cited publication in neuro-ophthalmology worldwide. Its editorial office has now moved from New York to Ann Arbor, Michigan, and a new editorial board has been formed.

In the coming years, we hope to maintain the quality of the journal, even enhance it. We will continue to venerate the case report. After all, a fascinating anecdote, supported by science and a good teaching point, is at the core of our specialty. We also hope to expand the publication of basic science research, clinical trials, and topical reviews that may have been prepared for meetings.

Electronic mail will allow us to hasten the review cycle. Eventually, we may handle all correspondence by e-mail. For the present, we still ask authors to send print copies of manuscripts and figures. However, we now offer authors the option of sending only one print copy of each figure, together with electronic figure files that we will copy and send to reviewers (we must still have at least one high-quality print of each figure to send to the publisher). We have simplified the instructions for authors, which appear, together with the copyright transfer form, on the JNO website (www.jneuro-ophthalmology.com) and in the print journal.

The March 2002 issue will sport a snazzy new cover. With the present issue, we have begun to subdivide the display of articles by category, as many other journals do. Look for these departments:

Original Contributions: includes basic science experiments, prospective or retrospective clinical investigations, and case reports

Photo Essays: observations based on interesting or unusual images

Letters: observations of less rigor than in original contributions and comments on previously published JNO articles

Reviews: essays that synthesize and analyze the significance of material on one or more topics, books, journal articles, meetings, or contributions in other media

Viewpoints: articles that reflect the authors' interpretation of one or more issues

Special Features: news of the activities of NANOS and its members, excerpts from NANOSNET, historical vignettes, interviews, and other unusual contributions

Editorials: commentaries on matters usually published in that journal issue

To prove that we have really entered the electronic communications era, the Journal of Neuro-Ophthalmology is now available online to subscribers at www.jneuro-ophthalmology.com. The online journal will offer the full text and graphics of issues beginning with the March 2001 (Vol. 21, No. 1) issue. New issues will be posted at the time of publication. Users will be able to browse issues, tables of contents, and author indexes; do full-text searches; and link from journal references to PubMed citations and abstracts. The table of contents and abstracts will be available to nonsubscribers, which should increase awareness of the journal.

Remember that the Journal of Neuro-Ophthalmology is the official archive of NANOS, a testament to its vitality. Send us your best work. We promise to review it more quickly and give you more space than the nonspecialty journals can offer.

Jonathan D. Trobe, MD
Editor-in-Chief
Paraneoplastic Optic Neuropathy and Cerebellar Ataxia With Small Cell Carcinoma of the Lung

Madhav R. Thambisetty, MD, DPhil, Clemens R. Scherzer, MD, Zhiya Yu, MD, PhD, Vanda A. Lennon, MD, PhD, and Nancy J. Newman, MD

Bilateral optic neuropathy and subacute cerebellar ataxia were manifestations of a paraneoplastic neurologic disorder in a woman found to have small cell carcinoma of the lung. Serologic tests revealed a neuronal autoantibody specific for CRMP-5, a 62-kd member of the collapsin response-mediating protein family. Unexplained optic neuropathy in the setting of subacute cerebellar ataxia should cause suspicion of a paraneoplastic disorder and prompt testing for this autoantibody, especially in patients at risk for lung carcinoma.

Key Words: Neuroimmunology—Oncology.

Paraneoplastic optic neuropathy is rare (1–5) but recognized with small cell lung carcinoma. Accompanying autoantibodies of neuronal (3,4) and oligodendrocyte (5) specificities have been reported. We report a patient with bilateral optic neuropathy and subacute cerebellar ataxia who was found to have small cell lung carcinoma and a serum autoantibody specific for a recently defined 62-kd neuronal antigen named collapsin response-mediating protein-5 (CRMP-5) (6).

CASE REPORT

A 72-year-old woman presented in May 1999 with bilateral reduction in visual acuity, progressive gait instability, and bilateral occipital headaches developing during the course of 2 weeks. Initial evaluation revealed bilaterally swollen optic nerves with best-corrected visual acuity of 20/60 OU. Neurologic examination results were normal except for gait instability. Computed tomography (CT) of the brain and orbits, with and without contrast, was unremarkable. Magnetic resonance imaging could not be obtained because of a pacemaker implanted for sick-sinus syndrome. Her erythrocyte sedimentation rate was 46 mm/h. Temporal artery biopsy results were normal, as were electromyography (including repetitive motor nerve stimulation) and nerve conduction studies. An electroretinogram (ERG) was not performed.

Past medical history was notable for hypertension, bilateral carotid endarterectomies, depression, and total abdominal hysterectomy 20 years earlier for benign pathology. Medications included trazodone, fluoxetine, verapamil, and aspirin. She had smoked cigarettes (40-pack-year history).

The patient’s visual acuity declined during several months, and she developed appendicular ataxia. Ophthalmologic examination in September 1999 revealed visual acuity of 20/200 OU and persistent bilateral optic disc edema. Lumbar puncture revealed a cerebrospinal fluid (CSF) opening pressure of 13 cm with 32 white blood cells (86% lymphocytes, 13% monocytes) and 130 mg/dL of protein (normal < 60 mg/dL). Syphilis serology and Venereal Disease Research Laboratories studies of CSF were nonreactive. Viral, fungal, and acid-fast bacillus culture results of CSF and serum were negative. Skin test results for tuberculosis immunity were negative. Radionuclide bone scan and chest radiograph were unremarkable.
By December 1999, the patient’s visual acuity had declined to 20/400 OU. She now had a left afferent pupillary defect, central scotomas in both visual fields, and bilateral disc edema without substantial arterial attenuation. She had hypophonia and dysphagia, requiring a gastrostomy tube for nutrition and was confined to bed by ataxia. Fine and rapidly alternating finger movements were impaired on the left, and she had mild dysmetria of the left arm and leg.

A lung nodule found by chest CT scan in the right upper lobe was identified as small cell carcinoma by CT-guided biopsy. Two CSF specimens were negative for malignant cells by cytologic examination. Serologic testing results for the carcinoma-associated retinopathy antibody were negative. A paraneoplastic autobody panel revealed P/Q-type calcium channel and CRMP-5 antibodies consistent with autoimmunity related to small cell lung carcinoma. Immunoprecipitation assays revealed P/Q-type calcium channel antibody (221 pmol/L; normal < 20 pmol/L). Immunofluorescence assays (7, 8) (at 1:60 dilution) were negative for type 1 Purkinje cell cytoplasmic antibody (PCA-1, or anti-Yo), PCA-2, PCA-Tr, ANNA-1 (or anti-Hu), ANNA-2 (or anti-Ri), and amphiphysin antibodies. However, an antineuronal IgG revealed that up to 1:30,720 dilution had the pattern of CRMP-5 autoantibody (6). In Western blots, the patient’s IgG bound to a 62-kd brain protein coinciding with the CRMP-5 band yielded by a positive control IgG, and to a recombinant human CRMP-5 protein (Gen-Bank #AF157634) but not to recombinant CRMP-2 or CRMP-3 proteins (6). In additional studies, (Fig. 1) the patient’s IgG bound to a 62-kd retinal protein, as did IgG in a CRMP-5–positive control patient’s serum (and a CRMP-5–specific monoclonal IgG (6) [data not shown]). After three cycles of plasmapheresis and two cycles of cisplatin and etoposide, the patient refused further chemotherapy. She died 3 months later.

**FIG. 1.** Proteins in aqueous extracts of rat brain and bovine retina, and a recombinant full-length human collapsin response-mediating protein-5 (CRMP-5) protein (Gen-Bank #AF157634) were probed by Western blot with sera from a CRMP-5–positive control patient, the patient of this report, and a healthy subject, all at 1:200 dilution. The molecular weight of each native heavy band is 62 kd.

**DISCUSSION**

Autoimmune paraneoplastic disorders of the central nervous system are mediated by antitumor immune responses directed against antigens common to a specific tumor (often occult) and the nervous system. The neurologic manifestations are varied and are not attributable to metastatic invasion of neural tissue by neoplastic cells. In the past decade, several IgGs specific for neuronal cytoplasmic and nuclear components have been defined as serologic markers of paraneoplastic neurologic autoimmunity. Those reflecting immune responses initiated by proteins in small cell lung carcinoma (ANNA-1, ANNA-2, PCA-2, amphiphysin, and CRMP-5) (6–8) are not found in healthy subjects, are lower in frequency and titer in patients with small cell lung carcinoma uncomplicated by a paraneoplastic neurologic disorder (9), and are more common with certain neurologic presentations than with others; however, no autobody is predictive of a discrete neurologic syndrome (8). Detection of one of these proteins suggests the autoimmune basis of the presenting neurologic disorder and focuses the search for a specific neoplasm.

Our patient had the rare paraneoplastic entity of optic neuropathy in combination with cerebellar ataxia and dysphagia. Her P/Q-type calcium channel antibody raises the possibility of unrecognized Lambert–Eaton syndrome, despite a negative EMG study. Another possibility includes the presence of P/Q-type calcium channel antibodies in the absence of Lambert–Eaton syndrome. Table 1 compares the clinical features reported in cases of paraneoplastic optic neuropathy with small cell lung cancer. All patients presented with visual loss (1–5). Disc edema was a presenting feature in all but one case (3). With one exception (2), there was concurrent cerebellar dysfunction. In all cases, lung carcinoma was found after the onset of visual symptoms.

The first autobody related to paraneoplastic optic neuropathy was described by Malik et al. (3) as an IgG that bound to neuronal and glial cytoplasm but not to systemic tissues. Unlike CRMP-5 IgG (6), it did not bind to the lung neoplasm. A second (named anti-CV2) was reported by De la Sayette et al. (5) as an IgG that bound to a 66-kd brain protein, earlier reported to be an oligodendrocyte-restricted antigen. A third was described by Luiz et al. (4) as an IgG that bound to a 60-kd protein expressed in retina, optic nerve, cerebellum, and cerebral cortex.

Unlike paraneoplastic optic neuropathy, several distinct autoantibodies have been described in cancer-associated retinopathy (CAR) syndrome (10). In the original description of the CAR syndrome, Thirkill et al. (11) reported the presence of serum autoantibodies against specific protein components of both retina and optic nerve.

Our patient’s serum contained two autobody markers of encephalomyeloneuropathy related to small cell lung carcinoma. The P/Q-type voltage-gated calcium channel antibody is most frequently found in patients with Lambert–Eaton myasthenic syndrome, but it is also
## TABLE 1. Comparison of clinical features of previously reported cases of paraneoplastic optic neuropathy with small cell carcinoma of the lung

<table>
<thead>
<tr>
<th>Author</th>
<th>Age/sex</th>
<th>Vision loss</th>
<th>Visual acuity</th>
<th>Visual fields</th>
<th>Fundus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pillay et al. (1) 1984</td>
<td>56/M</td>
<td>Gradually progressive, OU</td>
<td>20/100 OU</td>
<td>Not reported</td>
<td>Disc swelling OS</td>
</tr>
<tr>
<td>Boghen et al. (2), 1988</td>
<td>63/M</td>
<td>Acute, OD</td>
<td>3/200 OD</td>
<td>Central acotoma, inferior bundle defect OD</td>
<td>Disc swelling OD</td>
</tr>
<tr>
<td>Malik et al. (3), 1992</td>
<td>63/M</td>
<td>Gradually progressive, OU</td>
<td>20/200 OU</td>
<td>Cepoccenital scotomas, generalized constriction OU</td>
<td>Disc pallor, moderate arteriolar narrowing, marked AV nicking OU</td>
</tr>
<tr>
<td>Luiz et al. (4), 1998</td>
<td>59/F</td>
<td>Acute, OU</td>
<td>20/30 OD</td>
<td>Severe constriction OU</td>
<td>Disc edema OU</td>
</tr>
<tr>
<td>de la Sayette et al. (5), 1998</td>
<td>62/M</td>
<td>Acute, OS</td>
<td>20/400 OS</td>
<td>Central acotoma OS</td>
<td>Disc edema OU</td>
</tr>
<tr>
<td>Present report</td>
<td>72/F</td>
<td>Acute, OU</td>
<td>20/200 OU</td>
<td>Cepoccenital scotomas OU</td>
<td>Disc edema OU</td>
</tr>
</tbody>
</table>

* The diagnosis of “mixed bronchial carcinoma” is consistent with the common cellular origin of squamous cell, adenocarcinoma, and small cell carcinoma of the lung.

AV, antroventricular; CNS, central nervous system; EOM, extraocular movements; F, female; INO, internuclear ophthalmoplegia; M, male.

CRMP-5 autoantibody is particularly pertinent in a patient presenting with unexplained optic neuropathy, especially with early disc edema, with or without other neurologic signs. Diagnostic investigations for small cell carcinoma should be performed, particularly in patients with known risk factors for lung cancer.

### REFERENCES


### Clinical Course

<table>
<thead>
<tr>
<th>Limitation of adduction OU</th>
<th>Paralysis of upward gaze, mild limitation of horizontal gaze OU</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>VI, VII, IX, X palsies, internuclear ophthalmoplegia, dysarthria, intention tremor, dementia</td>
<td>Sensorimotor polyneuropathy, depression, intractability</td>
<td>Downbeat nystagmus, gait ataxia, intention tremor, truncal ataxia</td>
</tr>
<tr>
<td>Not reported</td>
<td>Not reported</td>
<td>IgG binding to neuronal and glial cytoplasm in human cortex, cerebellum, optic nerve</td>
</tr>
<tr>
<td>Pneumonectomy*</td>
<td>Tumor radiation</td>
<td>Medialinal radiation, systemic chemotherapy</td>
</tr>
<tr>
<td>Resolution of disc swelling, worsening visual acuity, persistent INO, death after 9 months from septic, visceral (but not CNS) metastases at autopsy</td>
<td>Stable visual ocular motor status, worsening of encephalitis, death after 9 months</td>
<td>Tumor remission at 6 months without change in neurologic and ophthalmologic status, death after 24 months from tumor recurrence</td>
</tr>
<tr>
<td>Improved visual acuity and visual fields, improved dysmetria and gait at 9 months, no radiologic evidence of tumor recurrence or metastases at 13 months</td>
<td>Improved speech and cerebellar symptoms, normal fundi without significant improvement in visual acuity at 1 month, no tumor recurrence at 2 years</td>
<td>Improved speech and cerebellar symptoms, normal fundi without significant improvement in visual acuity at 1 month, no tumor recurrence at 2 years</td>
</tr>
<tr>
<td>Improved speech and cerebellar symptoms, normal fundi without significant improvement in visual acuity at 1 month, no tumor recurrence at 2 years</td>
<td>Stable neurologic and ophthalmologic status 1 week after chemotherapy, death after 3 months</td>
<td></td>
</tr>
</tbody>
</table>

### References

The Photoreceptor Cell-Specific Nuclear Receptor is an Autoantigen of Paraneoplastic Retinopathy

Joseph G. Eichen, MS, Josep Dalmau, MD, PhD, Alexis Demopoulos, MD, Deborly Wade, BS, Jerome B. Posner, MD, and Myrna R. Rosenfeld, MD, PhD

Objectives: To report a novel antibody associated with paraneoplastic retinopathy and to characterize the retinal autoantigen.

Methods: Immunohistochemistry of rat and human tissues was used to identify antiretinal antibodies. Serologic screening of a bovine retinal cDNA expression library was performed to clone the target antigen.

Results: A 72-year-old woman presented with a 6-month history of progressive visual loss, bilateral central scotomas, light flashes, and night blindness. Visual acuity was 20/40 OD and 20/30 OS. There was generalized loss of retinal pigment and narrow arterioles; discs were normal in appearance. The electroretinogram showed no response. Chest computed tomography scan demonstrated a right lung mass; biopsy revealed poorly differentiated carcinoma. The patients' serum contained antibodies that immunolabeled nuclei of cells of the outer—and to a lesser extent, the inner—nuclear layer of the adult rat retina. No reactivity was identified with nonretinal adult human or rat tissues. Reactivity was seen in the developing rat embryo. Serologic screening of a bovine retinal library resulted in the isolation of three overlapping clones, encoding a protein highly homologous to the human photoreceptor cell-specific nuclear receptor gene product.

Conclusions: The target antigen of an antibody associated with paraneoplastic retinopathy is the photoreceptor cell-specific nuclear receptor, a member of a conserved family of nuclear receptors involved in photoreceptor cell development or maintenance.

Key Words: Cancer—Retinopathy—Paraneoplastic—Photoreceptor cell-specific nuclear receptor—Antibodies.

Paraneoplastic visual syndromes comprise a heterogeneous group of disorders involving retina and, less frequently, uvea and optic nerves (1-5). Some of these syndromes are associated with serum antibodies that specifically react with the subset of retinal cells undergoing degeneration, suggesting an immune-mediated pathogenesis (6,7). Studies with these antibodies have led to the identification of two retinal-specific target antigens, recoverin and tubby-like protein 1 (8,9). We report a patient with paraneoplastic retinopathy whose serum contained antiretinal antibodies against the photoreceptor-specific nuclear receptor gene product (PNR) (10).

Inherited mutations of the PNR gene (also known as NR2E3) have been found in patients with retinal degeneration associated with enhanced S-cone syndrome (ESCS), a disorder of retinal cell fate (11). In the mouse, deletions of the PNR homolog result in late-onset retinal degeneration (12). These data suggest that the retinal degeneration in our patient was likely caused by the immune-mediated knockout of PNR function.

PATIENT AND METHODS

Case report

For several months, a 72-year-old woman complained of transient black spots before her eyes, sensation of light flashes, and progressive decrease of vision that was worse at night. Her past medical history was unremarkable. Evaluations by several ophthalmologists revealed no pathology, and the diagnosis of hysterical blindness was considered. After 6 months of symptom...
development, a repeat evaluation demonstrated a corrected visual acuity of 20/40 OD and 20/30 OS. Extraocular motility was full. Pupils were 2.5 mm in bright light, normally reactive to light with no relative afferent defect. Goldmann visual fields were markedly constricted.

Ophthalmoscopy revealed narrow retinal arterioles and a generalized loss of pigment throughout the retina in both eyes; the optic discs had a normal appearance. A subsequent electroretinogram (ERG) showed absent photopic and scotopic responses OU. The rest of the neurologic and systemic examination results were normal, as was a magnetic resonance image (MRI) of the brain without and with contrast. Blood cell count and general chemistry were normal except for elevated lactate dehydrogenase (LDH) (279 U/L, normal 60–200 U/L). Chest CT showed a large right upper lobe paramediastinal mass with adjacent small nodules suspicious for bronchogenic tumor spread. A fine-needle aspirate of the lung mass showed poorly differentiated carcinoma. The patient refused treatment and was lost to follow-up.

**Sera and tissues**

The serum of the patient was obtained 6 months after the onset of visual symptoms; at this time, the ERG showed no responses. Control sera included four patients with paraneoplastic retinopathy associated with antirecoverin antibodies (3,8), three patients with melanoma-associated retinopathy (MAR) (5), ten patients without cancer with idiopathic (etiology unknown) retinopathy, eight patients with paraneoplastic syndromes of the central nervous system not involving the visual system (four with encephalomyelitis associated with anti-Hu antibodies (13), two patients with paraneoplastic cerebellar degeneration and anti-Yo antibodies (14), two patients with limbic encephalitis and anti-Ma2 antibodies (15), and 27 healthy people. Sera were stored at −70°C. Normal human and Wistar rat tissues were processed and stored as reported (16). Frozen bovine retina was obtained from Pel-Freeze, Inc. (Rogers, AR).

**Immunohistochemistry**

Frozen 7-μm-thick tissue sections were fixed in cold 30% methanol–70% acetone and incubated with patient’s serum (diluted 1:4,000) using an avidin–biotin peroxidase immunoassay, as reported (17,18). To avoid reactivity with endogenous IgG, all immunohistochemical studies with human tissues used IgG purified from patient sera and labeled with biotin (19). To determine whether the serum reactivity seen in immunohistochemical studies resulted from the expression of the cloned protein by retinal cells, sections of adult rat retina were incubated with the patient’s serum preabsorbed with the recombinant protein, as reported (15).

**Cloning, isolation, and sequence analysis**

The patient’s serum was used to screen a λ ZAP bovine retinal library (Stratagene, La Jolla, CA) at a density of 5 × 10⁵ pfu/150-mm plate of E. coli XL1-Blue (Stratagene) at 37°C. After a 6-hour incubation at 37°C, plates were overlaid with filters soaked in 10 mmol/L of isopropyl β-D-thiogalactopyranoside (IPTG) and incubated for 12 hours at 37°C. Filters were removed; blocked with 5% Blotto; incubated with the serum from the patient (1:4,000) for 2 hours at room temperature; washed in 50 mmol/L Tris (pH 7.4), 100 mmol/L NaCl, and 0.2% triton (TBST buffer); incubated at room temperature with [125I] protein A (0.1 μCi/mL) for 1 hour; washed with TBST; dried; and exposed to XAR5 film overnight at −70°C. Clones giving positive results were purified by several rounds of antibody screening until a yield of 100% positive plaques was obtained and then subcloned into pBluescript using the in vivo excision plaque rescue protocol (Stratagene).

Double-stranded cDNA was purified using the Qiagen (Santa Clarita, CA) plasmid midi-prep system and sequenced on both strands using an ABI 377 automated DNA sequencer and the dye terminator fluorescence method. T3, T7, and internal oligonucleotide primers were used.

**Western blot analysis**

Recombinant fusion proteins, E. coli proteins, and proteins from rat, bovine, and human tissues were obtained as previously described (18), resolved by 10% sodium dodecyl sulfate polyacrylamide gel electrophoresis, and transferred to nitrocellulose. The nitrocellulose strips were incubated with the patient’s sera (diluted 1:4,000), and the reactivity was demonstrated by an enhanced chemiluminescence method (Amersham, Arlington, IL) (16).

**RESULTS**

The serum of the patient contained antibodies (titer 1:500,000) that reacted with proteins expressed in the outer and inner nuclear layers of rat retina (Fig. 1). These autoantigens were not identified in nonretinal adult human or rat tissues (data not shown). Reactivity with human retinal tissue was not examined. In the developing rat, reactivity was identified in the migratory cells of the ventricular zone of the brain, the limb bud apical ectodermal ridge, and the lamina propria of the gut (E17) (data not shown).

Similar antibody reactivities were not demonstrated in the sera from patients with paraneoplastic retinopathy and recoverin antibodies, MAR, or in any of the other control and normal sera. In immunoblots of retinal protein extracts, no reactivity was found at 23 kd (compatible with recoverin reactivity) or at 37 to 40 kd (compatible with Hu reactivity) (8,17). The absence of recoverin antibodies was confirmed with immunoblots of recombinant recoverin protein (data not shown).

To determine the identity of the target retinal protein of these autoantibodies, we screened a bovine retinal cDNA expression library and isolated three clones, called De1, De2, and De3 (Fig. 2). Sequence analysis demonstrated that De1 contained a complete open reading frame coding for a 46.5-kd protein. De2 and De3 contained the same sequences but lacked varying amounts of the 5′ terminal region. De3 also contained additional 3′ sequence. The three cDNA sequences were...
FIG. 1. Immunohistochemical analysis of the patients’ serum with rat retina. Section of rat retina incubated with the patient’s serum antibodies demonstrates immunolabelling of the outer nuclear (ONL) and inner nuclear layers (INL). No reactivity is seen with the photoreceptor (PR), outer plexiform (OPL), inner plexiform (IPL), and the ganglion cell layers (GCL) (hematoxylin counterstain, x400).

combined into a consensus cDNA sequence that was used in a homology search of GenBank databases (Bethesda, MD). This search revealed almost complete identity to the recently described human retinal-specific gene, PNR (AF121129) (10), with the exception of the presence of a bovine-specific short interspersed element (SINE) (20) near the 3′ end of the De clones.

Western blots of recombinant proteins derived from the De1, De2, and De3 clones revealed that the patients’ serum recognized all three fusion proteins. Based on the homology alignment of the three clones with PNR (Fig. 2), these data suggest that the immunodominant epitope does not reside in the zinc-finger domain, which is lacking in De2, but could reside in the ligand-binding domain. None of the control or normal sera demonstrated reactivity with any of the three De recombinant proteins.

Preabsorption of serum antibodies with Del resulted in abrogation of serum reactivity with retina, indicating that Del and retina express similar epitopes (Fig. 3).

**DISCUSSION**

In this article, we demonstrate that the retinal-specific protein PNR is the target antigen of the autoimmune response in a patient with paraneoplastic retinopathy. The paraneoplastic retinopathies are a group of syndromes characterized by cone or rod dysfunction associated with photosensitivity, progressive loss of vision and color perception, central or ring scotomas, night blindness, and attenuation of photopic and scotopic responses in the ERG (1,2,21,22). Patients with paraneoplastic retinopathy often develop recoverin antibodies and suffer from a small cell lung cancer (SCLC), although other tumors have been reported (7,21,23–25). Recoverin antibodies have also been detected in the serum of patients without cancer but with a clinically similar retinopathy (26,27). In these cases, the immunologic staining pattern is diffuse and suggests an interaction with multiple non-specific retinal antigens (26). There are reports of patients with paraneoplastic retinopathy and antibodies to human enolase (28) or neurofilaments (29), although recent studies have suggested that these are not specific immune responses (30). Patients with melanoma can develop a paraneoplastic retinopathy, MAR, associated with serum antibodies directed against an unknown antigen localized to bipolar cells (31,32).

Our patient’s symptoms were similar to those reported in paraneoplastic retinopathy associated with antirecoverin antibodies, but the serum contained antibodies that targeted PNR. The PNR gene product is a member of the nuclear receptor superfamily (33,34). Nuclear receptors are ligand-dependent transcription factors that mediate a wide variety of physiologic and regulatory processes. Many nuclear receptors, including PNR, are orphan receptors with unknown ligands. The PNR gene is closely
related to the TLX gene, the human homolog of the Drosophila terminal gap gene tailless, which plays an essential role in fly eye development (35). A remarkable feature of PNR is its highly restricted expression in the retina. Kobayashi et al. (10) reported expression limited to the outer nuclear layer, whereas Chen et al. (36) found expression in the inner nuclear layer and retinal pigment epithelium. Our study suggests that PNR is expressed in the inner and outer nuclear layers of adult rat retina. Determination of the exact site of the immune response in our patient, however, would require studies with human retinal tissue. Highly restricted expression patterns are relatively unique among transcription factors and have only been demonstrated for ERX and CRX (37,38). CRX is essential for the maintenance of mammalian photoreceptors and, in humans, represents a gene responsible for the autosomal dominant cone and rod dystrophy, CORDII (37,39). Interestingly, a potential CRX binding site has been noted upstream of the PNR promoter, suggesting regulation of PNR expression by CRX.

Studies suggest that PNR is likely involved in suppressing genes whose expression is refractory to photoreceptor function (10,12). The pattern of expression in the developing rat embryo found in this study also suggests a role in early development of neural and nonneural structures.

Finding PNR mutations in a cohort of patients with ESCS demonstrates that PNR is important in retinal function (11). Patients with ESCS develop enhanced sensitivity to blue light because of increased numbers of S cones and eventually progress to retinal degeneration (40,41). A deletion of the mouse PNR homolog is the cause of retinal degeneration in the rd7 mouse, a model of hereditary retinal degeneration (12).

These data suggest a mechanism whereby anti-PNR antibodies interfere with PNR function, leading to retinal degeneration. This mechanism could occur by blockade of ligand binding, because our data suggest that the antibody recognition site may reside within the ligand-binding domain. This would be similar to several paraneoplastic syndromes of the peripheral nervous system, such as the Lambert–Eaton myasthenic syndrome associated with anti-voltage-gated calcium channel antibodies (42) and myasthenia gravis associated with anti-acetylcholine receptor antibodies (43).

Alternatively, the occurrence of high-titer anti-PNR antibodies in the serum of our patient could represent an immunologic reaction against antigens released by retinal cells damaged by unknown mechanisms. In this case, one would expect the patient to also have serum antibodies against other highly immunogenic retinal proteins (such as recoverin or Hu), which were not found in our patient (8,44). More likely, the presence of PNR antibodies resulted from an immunologic reaction triggered by the tumor. The exact mechanisms of how a tumor breaks immune tolerance for retinal or neuronal proteins is unknown, but for other models of paraneoplastic syndromes (i.e., anti-recoverin-associated retinopathy, anti-Hu or anti-Yo central nervous system syndromes), the associated tumors express the retinal or neuronal target antigens (44,45). In our patient, no tumor was available for antigen studies.

Our findings indicate that PNR is a novel autoantigen of paraneoplastic retinopathy. Future studies should be aimed at elucidating the pathogenicity of the antibodies and the possible role of T-cell responses.

Acknowledgments: The authors thank Dr. C. Kane for reviewing the immunohistochemical studies of the developing rat embryo and Dr. C. Thirkill for providing serum samples.

REFERENCES


Clinical and Immunologic Characteristics of Melanoma-Associated Retinopathy Syndrome: Eleven New Cases and a Review of 51 Previously Published Cases

John L. Keltner, MD, Charles E. Thirkill, PhD, and Peter T. Yip, MD

Objective: To evaluate the signs, symptoms, and immune responses of patients with melanoma-associated retinopathy (MAR) syndrome.

Materials and Methods: We reviewed the clinical and immunologic findings of 62 MAR syndrome patients. They include 25 patients from our institution (11 not previously reported) and 37 patients reported from other institutions.

Results: There were 33 men and seven women (no gender information is available for the remaining 22 cases). Age at onset of the visual disturbance averaged 57.5 years (range, 30-78). Visual acuity of 20/60 or better was initially present in 82%. Fundus examination was normal in 44%, optic disc pallor was present in 23%, and retinal vessel attenuation was present in 30% Vitreous cells were present in 30%. The latency from melanoma diagnosis to recognition of MAR syndrome averaged 3.6 years (range, 2 months to 19 years). Seven patients sustained visual improvement with various treatment regimens, especially with intravenous immunoglobulin and cytoreductive surgery (metastasectomy). Indirect immunohistochemical staining of the bipolar layer was typical, but several other retinal elements were also reactive. Tissue from a metastatic melanoma excised from one of the patients expressed antigens that reacted with antiretinal antibodies.

Conclusion: MAR syndrome demonstrates diverse clinical and immunologic features. Treatment, especially intravenous immunoglobulin and cytoreductive surgery (metastasectomy), improves vision in some cases.

Key Words: Melanoma-associated retinopathy—Immunology—Photopsia—Antiretinal antibodies—Intravenous immunoglobulin treatment.

Paraneoplastic syndromes result from the immunologic effects of cancer located remote from the affected organ. With respect to vision loss, cancer-associated retinopathy (CAR) (1-9) and melanoma-associated retinopathy (MAR) (1,10-39) are now well-recognized entities. A lesser recognized entity is autoimmune-related retinopathy and optic neuropathy (ARRON) syndrome, in which patients have no evidence of cancer (40-45).

CAR syndrome is a paraneoplastic retinal degeneration often associated with small cell carcinoma of the lung but is also described in patients with gynecologic, breast, endocrine, and other malignancies. It involves antibodies against retinal elements and causes both rod and cone dysfunction. Although the 23-kd photoreceptor protein recoverin was the first and the most common retinal antigen linked to CAR syndrome, more than 15 other proteins expressed by rods, cones, and ganglion cells of the retina are now thought to act as potential autoantigens (45). In many cases, the CAR antigen is also expressed by the patient’s cancer. Visual loss in CAR syndrome is marked by photopsias, progresses over several months, and frequently precedes the discovery of the primary cancer. Features associated with cone dysfunction are photosensitivity, abnormal visual acuity, color vision abnormalities, central scotomas, and an abnormal cone-mediated electroretinogram (ERG). Features associated with rod dysfunction are nyctalopia, prolonged dark adaptation, peripheral or ring scotomas, and an abnormal rod-mediated ERG (1-9).

ARRON syndrome describes patients with autoimmune-related retinopathy and optic neuropathy who do not have evidence of cancer. They may have optic disc pallor, retinopathic changes, progressive visual field and visual acuity loss, and an abnormal ERG resembling...
that of patients with CAR syndrome. However, these features develop more slowly. ARRON patients often have systemic autoimmune disorders. They may develop one or multiple autoantibodies against elements in the retina and/or optic nerve. Various investigators have reported ARRON patients with autoantibodies directed against the inner plexiform layer—35-kd retinal Müller cell antigen, 23-kd recoverin protein (not related to cancer), and a 22-kd neuronal antigen in the retina and optic nerve (40–45). Other investigators have found noncancer-related, progressive panretinal degeneration with CAR-like clinical changes and antibodies to several retinal proteins (44). It is unclear whether the autoimmune serologic reactions cause visual loss or are simply epiphenomena.

In the retinal degeneration associated with cutaneous melanoma—MAR syndrome—patients frequently have an established diagnosis of cutaneous melanoma and develop vision problems years later, usually associated with monococular metastasis. Patients frequently describe the sudden onset of shimmering, flickering, or pulsating photopsias and difficulty seeing in the dark, together with progressive visual loss over several months (1,10–39). The ERG reveals a characteristic pattern of a markedly reduced B wave, indicating compromised bipolar cell function, and a normal dark-adapted A wave (negative appearance), indicating normal photoreceptor cell function. Similar ERG findings are observed in congenital stationary night blindness (CSNB). The characteristic immunohistochemical autoimmune response involves antigens located within the bipolar layer, where horizontal and amacrine cells intermingle with axons of Müller's glia (1,10–39). This immunologic reaction differs from that of CAR in that the associated antigens are not readily identifiable in Western blot reactions on extracts of retina. The antigens involved are either small quantities of proteins, proteoglycans (16), lipids (16,20), or carbohydrates.

As with other paraneoplastic retinopathies, MAR syndrome is rare (10–39). Because some authors have reported the same case more than once, the exact number of reported cases is difficult to determine. We have serum samples from 25 MAR patients, collected from 1992 to 2000. Features of 14 of these cases have been previously documented; 11 cases are described here for the first time. In this report, we add the features of these 11 cases to the 51 cases previously reported.

METHODS

We evaluated the 11 previously unreported MAR patients at the University of California, Davis Ophthalmology Research Laboratory by Western blot analysis on an extract of whole rhesus monkey retina and indirect immunohistochemistry on sectioned rhesus monkey eyes. The details of these tests were previously described (5,46).

Inclusion criteria for MAR syndrome were a history of malignant melanoma and antibody reactions to retinal cells in the bipolar layer. Clinical symptoms and ERG changes suggestive of MAR syndrome were used to confirm the diagnosis when available. We compared the clinical and immunologic features of our new cases to those of previously reported cases fulfilling the same inclusion criteria.

A formalin-fixed and paraffin-embedded metastatic melanoma removed from the left axilla of patient 58 (Table 1) was evaluated for immunologic activity with rabbit anti-whole bovine retina serum. Six-micron sections of the melanoma were made. These sections were deparaffinized in xylene and brought through ethanol to saline where they were exposed to a 1:10 dilution of rabbit anti-whole bovine retina serum overnight at 4°C. The rabbit anti-retina antibody localization on specific components of the melanoma was visualized using fluorescein-isothiocyanate conjugated goat anti-rabbit polyclonal gamma globulins, at a dilution of 1:200. After a thorough wash in phosphate-buffered saline–Tween, sections were mounted in 50% glycerol in saline and then examined and photographed at a final magnification of 200x.

Because the information in this study is recorded and presented such that subjects cannot be identified, exemption from review was approved by the Human Subjects Review Committee, Office of the Vice Chancellor for Research, the University of California, Davis Medical Center.

RESULTS

Clinical information from all known cases of MAR patients is summarized chronologically in Tables 1 and 2. Clinical characteristics are tabulated in Tables 3 through 10. Previously reported cases are listed as patients 1 through 51. The newly reported patients from our institution are patients 52 through 62. In the tables, we have lumped the previously reported and newly reported cases from our institution as UC Davis (25 serum samples) cases and referred to all other patients as patients from other institutions.

Age and gender

The average age was 57.5 years (range, 30–78). There were 33 men and seven women (no gender information is available for the remaining cases) (Table 3).

Presenting visual acuity

Visual acuity at presentation was 20/60 or better in 28 (82%) of 34 patients for whom such data were available. In six of these 34 patients at presentation, moderate to severe visual loss (20/200 or worse) was present in one or both eyes. In nine of 20 patients, the last recorded visual acuity demonstrated moderate to severe visual loss (20/200 or worse) in one or both eyes (Table 4).

Presenting visual fields

Visual fields showed generalized constriction in 18 of 27 patients where such information was available. Eighteen of 27 had central or paracentral scotomas or depressions, and six of 27 had arcuate visual field defects (Table 5).

Presenting fundus findings

The fundus was normal in 19 (44%) of 43 patients where such information was available (Table 6).
<table>
<thead>
<tr>
<th>Patient no./authors</th>
<th>Age/ gender</th>
<th>VA initial</th>
<th>VF</th>
<th>Fundus</th>
<th>Vitreous</th>
<th>ERG pattern</th>
<th>Last recorded visual data</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Gass, 1984)</td>
<td>71/F</td>
<td>OD LP, OS LP</td>
<td>—</td>
<td>Multiple yellow-white depigmentation in juxtapapillary and parafoveal areas, optic nerves swollen, arteriolar attenuation, OU</td>
<td>2+ aqueous cells and flare, vitreous cells OU</td>
<td>Extinguished OU</td>
<td>OD 2/1000, OS 6/200</td>
</tr>
<tr>
<td>2 (Ripp et al., 1984)</td>
<td>30/M</td>
<td>OD 20/20, OS 20/20</td>
<td>Slight depression OU</td>
<td>Normal OU</td>
<td>—</td>
<td>CSNB</td>
<td>—</td>
</tr>
<tr>
<td>3 (Makows et al., 1988)</td>
<td>38/M</td>
<td>OD 20/20, OS 20/20</td>
<td>Constricted peripheral VF OU, OD Henner-Behrems depression, OS paracentral scotoma</td>
<td>—</td>
<td>Arteriolar attenuation OU</td>
<td>—</td>
<td>CSNB</td>
</tr>
<tr>
<td>4 (Berson and Lessell, 1988)</td>
<td>69/M</td>
<td>OD 20/20, OS 20/20</td>
<td>Mild depression OU</td>
<td>Occasional window defects in RPE OU</td>
<td>—</td>
<td>CSNB</td>
<td>OD 20/25, OS 20/25, no change in ERG</td>
</tr>
<tr>
<td>5 (Alexander et al., 1992)</td>
<td>58/M</td>
<td>OD 20/20, OS 20/20</td>
<td>OD enlarged blind spot, parafoveal scotoma, OS normal</td>
<td>—</td>
<td>—</td>
<td>CSNB</td>
<td>—</td>
</tr>
<tr>
<td>6 (MacKay et al., 1992)</td>
<td>63/M</td>
<td>OD 20/20, OS 20/20</td>
<td>Slight depression OU</td>
<td>Constricted peripheral VF</td>
<td>—</td>
<td>CSNB</td>
<td>—</td>
</tr>
<tr>
<td>7-9 (Pollock et al., 1992)</td>
<td>3 cases</td>
<td>OD 20/20, OS 20/20</td>
<td>Slight depression OU</td>
<td>Arteriolar attenuation OU</td>
<td>—</td>
<td>CSNB</td>
<td>—</td>
</tr>
<tr>
<td>10 (Milam et al., 1993)</td>
<td>36/M</td>
<td>OD 20/20, OS 20/20</td>
<td>Central depression OU</td>
<td>RPE mottling in the midperiphery, arteries slightly attenuated OU</td>
<td>OU fine vitreous cells</td>
<td>CSNB</td>
<td>Decreased haze and improved GMVF OU</td>
</tr>
<tr>
<td>11 (Rush et al., 1993)</td>
<td>50/M</td>
<td>OD 20/20, OS 20/20</td>
<td>OD general depression and retinal edema, OS acute macular defects</td>
<td>Arteriolar attenuation OU</td>
<td>—</td>
<td>CSNB</td>
<td>Progressive VF loss OU</td>
</tr>
<tr>
<td>12 (Andreson et al., 1993)</td>
<td>48/M</td>
<td>OD 20/20, OS 20/20</td>
<td>No peripheral constriction with WVE on GVF OU</td>
<td>Normal OU</td>
<td>—</td>
<td>CSNB</td>
<td>—</td>
</tr>
<tr>
<td>13, 14 (Weinstein et al., 1994)</td>
<td>46/F</td>
<td>OD 20/20</td>
<td>Central scotomas, constriction OU</td>
<td>Optic nerve palor, vessel attenuation OU</td>
<td>—</td>
<td>CSNB</td>
<td>OU 1/200</td>
</tr>
<tr>
<td>15-17 (Kim et al., 1994)</td>
<td>61/M</td>
<td>OD 20/20, OS 20/20</td>
<td>OD pseudovegetative glaucoma, 0.5 cup/disc, OS normal</td>
<td>Normal OU</td>
<td>—</td>
<td>CSNB</td>
<td>OD 20/20, OS 20/70</td>
</tr>
<tr>
<td>18-27 (Milam, 1995)</td>
<td>10 cases</td>
<td>OD 20/20</td>
<td>Central scotomas, constriction OU</td>
<td>Optic nerve palor, vessel attenuation OU</td>
<td>—</td>
<td>CSNB</td>
<td>OU 1/200</td>
</tr>
<tr>
<td>28 (Remolli et al., 1995)</td>
<td>52/M</td>
<td>OD 20/20, OS 20/20</td>
<td>Central scotomas, constriction, enlarged blind spots OU</td>
<td>Normal OU</td>
<td>—</td>
<td>CSNB</td>
<td>OD 6/200, OS 20/40</td>
</tr>
<tr>
<td>29 (Singh et al., 1995)</td>
<td>64/M</td>
<td>OD 20/20, OS 20/20</td>
<td>Central scotomas, constriction, enlarged blind spots OU</td>
<td>Optic nerve palor, vessel attenuation, RPE pigment mosaicism OU</td>
<td>2-3+ vitreous cells, retinal periphereal OU</td>
<td>CSNB</td>
<td>OA stable for 12 mo</td>
</tr>
<tr>
<td>30 (Koller et al., 1995)</td>
<td>44/M</td>
<td>OD 20/20, OS 20/20</td>
<td>OD pericentral scotoma, OS central scotomas, OS pericentral scotomas</td>
<td>Normal OU and vitreous haze, RPE loss OU</td>
<td>—</td>
<td>CSNB</td>
<td>OD 20/400, OS 20/400</td>
</tr>
<tr>
<td>31 (Duk et al., 1996)</td>
<td>62/M</td>
<td>OD 20/20, OS 20/20</td>
<td>Central scotomas, constriction, enlarged blind spots OU</td>
<td>Normal OU</td>
<td>—</td>
<td>CSNB</td>
<td>OD 20/400, OS 20/400</td>
</tr>
<tr>
<td>32 (Remolli et al., 1995)</td>
<td>61/M</td>
<td>OD 20/20, OS 20/20</td>
<td>OD normal, OS tubular field</td>
<td>Optic nerve palor, vessel attenuation OU</td>
<td>—</td>
<td>CSNB</td>
<td>OD 20/25, OS 20/50</td>
</tr>
<tr>
<td>33, 34 (Duk et al., 1996)</td>
<td>50/M</td>
<td>OD 20/20, OS 20/20</td>
<td>Normal OU</td>
<td>Normal OU</td>
<td>—</td>
<td>CSNB</td>
<td>—</td>
</tr>
<tr>
<td>35, 36 (Duk et al., 1996)</td>
<td>50/M</td>
<td>OD 20/20, OS 20/20</td>
<td>OD normal, OS tubular field</td>
<td>Normal OU</td>
<td>—</td>
<td>CSNB</td>
<td>—</td>
</tr>
</tbody>
</table>

*Note: OU = OD, OS = OD.*
TABLE 1. Continued

<table>
<thead>
<tr>
<th>Patient no/Authors</th>
<th>Age/ gender</th>
<th>VA initial</th>
<th>VF</th>
<th>Fundus</th>
<th>Venoms</th>
<th>ERG pattern</th>
<th>Last recorded visual data</th>
</tr>
</thead>
<tbody>
<tr>
<td>59/ Kralik et al., 1997</td>
<td>60 M</td>
<td>OD 20/60, OS 20/60</td>
<td>Aracne defects OU</td>
<td>Normal OU</td>
<td>—</td>
<td>OD normal, OS CSNB</td>
<td>No improvement</td>
</tr>
<tr>
<td>34/ Bock et al., 1997</td>
<td>51 M</td>
<td>OD 20/60, OS 20/60</td>
<td>Marked constriction OU</td>
<td>Normal OU</td>
<td>—</td>
<td>CSNB</td>
<td>No improvement</td>
</tr>
<tr>
<td>35/ Hopfinger et al., 1997</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>36/ Glitner and Smith, 1999 (22)</td>
<td>59 M</td>
<td>OD 20/30, OS 6/20</td>
<td>OD constriction, OS constriction and central scotoma</td>
<td>Optic nerves pale, blonde fundus with fine macular drusen OU</td>
<td>—</td>
<td>CSNB</td>
<td>No change in vision</td>
</tr>
<tr>
<td>37/ Fender et al., 1999 (33)</td>
<td>61 M</td>
<td>OD 10/200, OS 20/200</td>
<td>Central scotomas, peripheral constriction OU</td>
<td>Optic nerves pale, vessels attenuated, macular RPE change OU</td>
<td>—</td>
<td>CSNB</td>
<td>OD 4/200, OS 1/200</td>
</tr>
<tr>
<td>38/ McCoy and Hedges, 1999 (34)</td>
<td>55 M</td>
<td>OD 3/20, OS 20/60</td>
<td>OD peripapillary scotoma, OS central depression</td>
<td>Normal OU</td>
<td>—</td>
<td>CSNB</td>
<td>Improved GMVF and ERG OD</td>
</tr>
<tr>
<td>39/ Lei et al., 2000</td>
<td>1 case</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>40/ Vaglianos et al., 2000 (35)</td>
<td>57 F</td>
<td>OD 20/25, OS 20/25</td>
<td>Cystoid OU</td>
<td>OD normal, OS anomalous optic disk vasculature</td>
<td>—</td>
<td>CSNB</td>
<td>OD 20/25, OS 20/20</td>
</tr>
<tr>
<td>41/ Felds et al., 2000</td>
<td>67 M</td>
<td>OD 20/25, OS 20/25</td>
<td>Constriction, central, and peripapillary scotoma OU</td>
<td>Normal OU</td>
<td>—</td>
<td>CSNB</td>
<td>No improvement</td>
</tr>
<tr>
<td>42/ Fujin et al., 2000</td>
<td>1 case</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>43/ Holder, 2000 (36)</td>
<td>7 cases</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>44/ Stauss, 2001</td>
<td>51 M</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>45/ Steinhaus et al., 2001 (37)</td>
<td>62 M</td>
<td>77 M</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>52/ UC Davis patient 1</td>
<td>59 F</td>
<td>OD 20/25, OS 20/20</td>
<td>Central scotomas OU</td>
<td>Optic nerves pale, vessels attenuated OU</td>
<td>2+ cells OD, 1+ cells OS</td>
<td>CSNB</td>
<td>Return of color vision, scotomas smaller, improved VF and dark adaptation</td>
</tr>
<tr>
<td>53/ UC Davis patient 2</td>
<td>60 M</td>
<td>OD CF 3', OS CF 3'</td>
<td>Central scotomas, marked constriction OU</td>
<td>Optic nerves pale OU</td>
<td>3+ cells OU</td>
<td>CSNB</td>
<td>CME OU</td>
</tr>
<tr>
<td>54/ UC Davis patient 3</td>
<td>70 F</td>
<td>OD 20/60, OS 20/60</td>
<td>Central scotomas, central defects, constriction OU</td>
<td>Optic nerves pale, vessels attenuated, macular RPE change OU</td>
<td>—</td>
<td>—</td>
<td>OD 20/20, OS 20/20</td>
</tr>
<tr>
<td>55/ UC Davis patient 4</td>
<td>47 M</td>
<td>OD 20/60, OS 20/60</td>
<td>Constriction OS &gt; OD</td>
<td>Optic nerves pale, vessels attenuation, macular RPE changes OU</td>
<td>—</td>
<td>—</td>
<td>OD 20/20, OS 20/20</td>
</tr>
<tr>
<td>56/ UC Davis patient 5</td>
<td>76 F</td>
<td>OD 20/30, OS 20/60</td>
<td>Cystoid OU</td>
<td>Optic nerves pale OU</td>
<td>—</td>
<td>CSNB</td>
<td>OD 20/60, OS 20/60, VF expanded and back to baseline</td>
</tr>
<tr>
<td>57/ UC Davis patient 6</td>
<td>42 M</td>
<td>OD 20/20, OS 20/20</td>
<td>OD macular defects and constriction, OS double arcuate defect and constriction</td>
<td>Normal OU</td>
<td>—</td>
<td>ERG almost extinguished</td>
<td>OD 20/20, OS 20/20, Improved VFs</td>
</tr>
<tr>
<td>58/ UC Davis patient 7</td>
<td>75 M</td>
<td>OD 20/20, OS 20/20</td>
<td>Mild optic nerve palsy, RPE changes OU</td>
<td>Trace cells OD</td>
<td>—</td>
<td>CSNB</td>
<td>Improved VFs and visual symptoms</td>
</tr>
<tr>
<td>59/ UC Davis patient</td>
<td>888</td>
<td>—</td>
<td>—</td>
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<td>60/ UC Davis patient</td>
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<td>61/ UC Davis patient</td>
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<td>—</td>
</tr>
<tr>
<td>62/ UC Davis patient</td>
<td>1888</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

* Pollock, et al., Melanoma-associated retinopathy (MAR), presented as a poster at the NOSOS meeting, 1992.
† Two cases reported. One of them had been reported previously by Alexander et al., 1993 (14).
‡ Twelve cases reported. Two of these had been reported previously by Alexander et al., 1992 (14) and Milton et al., 1993 (16).
§ One case reported. It had been reported previously by Rougier et al., 1995 (24).
¶ One case reported. It had been reported previously by Boeck et al., 1997 (30).
‖ Three cases reported. Two of them had been reported by Kim et al., 1994 (21) and Kellner et al., 1995 (23); one is new and without clinical information.
§§ Twenty-three patients were reported to be suspicious for MAR syndrome in the ARVO 2000 abstract. Through personal communication with Dr. Arno Haus, Heidelberg, Germany, we learned that only three of these patients had antiretinal antibody activities in their sera and met the inclusion criteria for MAR syndrome.
*** serum samples only, no clinical information.
ARMd, age-related macular degeneration; CF, Count Fingers; CME, cystic macular edema; CSNB, congenital stationary night blindness; ERG, electroretinogram; GMVF, Goldmann visual field; PRN, posterior limitis optic neuropathy; RPE, retinal pigment epithelium; VA, visual acuity; VF, visual field.

### TABLE 2. Nonophthalmic features of reported melanoma-associated retinopathy (MAR) cases

<table>
<thead>
<tr>
<th>Patient no./authors</th>
<th>Melanoma to metastasis (y)</th>
<th>Melanoma to MAR (y)</th>
<th>Melanoma to survival (y)</th>
<th>Melanoma treatment</th>
<th>MAR treatment</th>
<th>Serum analyzed at UC Davis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/Gass, 1984 (10)</td>
<td>3</td>
<td>3</td>
<td>5.1 (died)</td>
<td>Surgery</td>
<td>Prednisone 80 mg</td>
<td>No</td>
</tr>
<tr>
<td>2/Ripps et al., 1984 (11)</td>
<td></td>
<td>1.5</td>
<td>2.5 (died)</td>
<td>Surgery and chemo</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>3/DuBois et al., 1988 (12)</td>
<td></td>
<td>2.5</td>
<td></td>
<td>Surgery and chemo</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>4/Berson and Lessell, 1988 (13)</td>
<td></td>
<td></td>
<td></td>
<td>Surgery and chemo</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>5/Alexander et al., 1992 (14)</td>
<td></td>
<td></td>
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<td>Surgery and chemo</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>6/MacKay et al., 1992 (15)</td>
<td></td>
<td></td>
<td></td>
<td>Surgery and chemo</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>7-9/Pollock et al., 1992*</td>
<td></td>
<td></td>
<td></td>
<td>Surgery and chemo</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>10/Milam et al., 1993 (16)</td>
<td></td>
<td></td>
<td></td>
<td>Surgery and chemo</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>11/Rush et al., 1993 (17)</td>
<td></td>
<td></td>
<td></td>
<td>Surgery and chemo</td>
<td>None</td>
<td>No</td>
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<tr>
<td>12/Andreasson et al., 1993 (18)</td>
<td></td>
<td></td>
<td></td>
<td>Surgery and chemo</td>
<td>None</td>
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<tr>
<td>13/Weinstein et al., 1994 (19)</td>
<td></td>
<td></td>
<td></td>
<td>Surgery and chemo</td>
<td>None</td>
<td>No</td>
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<tr>
<td>14-17/Kim et al., 1994 (21)</td>
<td></td>
<td></td>
<td></td>
<td>Surgery and chemo</td>
<td>None</td>
<td>No</td>
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<tr>
<td>18-27/Milam, 1995 (20)</td>
<td></td>
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<td>Surgery and chemo</td>
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<td>No</td>
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<tr>
<td>28/Rentullo et al., 1995 (26)</td>
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<td>None</td>
<td>No</td>
</tr>
<tr>
<td>29/Singh et al., 1995 (27)</td>
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<td></td>
<td>Surgery and chemo</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>30/Hoffer et al., 1995 (28)</td>
<td></td>
<td></td>
<td></td>
<td>Surgery and chemo</td>
<td>None</td>
<td>No</td>
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<tr>
<td>31/Pollock et al., 1995 (33)</td>
<td></td>
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<td></td>
<td>Surgery and chemo</td>
<td>None</td>
<td>No</td>
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<tr>
<td>32/Loew et al., 1996 (34)</td>
<td></td>
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<td>Surgery and chemo</td>
<td>None</td>
<td>No</td>
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<tr>
<td>33/Kindl et al., 1997 (36)</td>
<td></td>
<td></td>
<td></td>
<td>Surgery and chemo</td>
<td>None</td>
<td>No</td>
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<tr>
<td>34/Boeck et al., 1997 (38)</td>
<td></td>
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<td></td>
<td>Surgery and chemo</td>
<td>None</td>
<td>No</td>
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<tr>
<td>35/Vaphiades et al., 1997 (39)</td>
<td></td>
<td></td>
<td></td>
<td>Surgery and chemo</td>
<td>None</td>
<td>No</td>
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<tr>
<td>36/Leunig and Hedges, 1999 (39)</td>
<td></td>
<td></td>
<td></td>
<td>Surgery and chemo</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>37/Pott et al., 1999 (40)</td>
<td></td>
<td></td>
<td></td>
<td>Surgery and chemo</td>
<td>None</td>
<td>No</td>
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<tr>
<td>38/Leunig et al., 2000 (41)</td>
<td></td>
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<td>Surgery and chemo</td>
<td>None</td>
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<tr>
<td>39/Yaphiades et al., 2000 (42)</td>
<td></td>
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<td>Surgery and chemo</td>
<td>None</td>
<td>No</td>
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<tr>
<td>40/Flynn et al., 2000 (43)</td>
<td></td>
<td></td>
<td></td>
<td>Surgery and chemo</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>41/Flynn et al., 2000 (44)</td>
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<td></td>
<td>Surgery and chemo</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>42-49/Glauser, 2000 (33)</td>
<td></td>
<td></td>
<td></td>
<td>Surgery and chemo</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>50-51/Klauser et al., 2000 (46)</td>
<td></td>
<td></td>
<td></td>
<td>Surgery and chemo</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>52-55/UC Davis patient 1</td>
<td></td>
<td></td>
<td></td>
<td>Surgery and chemo</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>56-58/UC Davis patient 2</td>
<td></td>
<td></td>
<td></td>
<td>Surgery and chemo</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>59-60/UC Davis patient 3</td>
<td></td>
<td></td>
<td></td>
<td>Surgery and chemo</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>61-63/UC Davis patient 4</td>
<td></td>
<td></td>
<td></td>
<td>Surgery and chemo</td>
<td>None</td>
<td>No</td>
</tr>
</tbody>
</table>
Optic nerve pallor, vessel attenuation, retinal pigment epithelial changes, and vitreous cells were seen in a number of patients. One patient had marked retinal periphlebitis (26).

**Electroretinography**

The ERGs of 54 of 56 patients for whom such data were available exhibited a markedly reduced B wave and a normal dark-adapted A wave (Table 7). Similar ERG findings are seen in patients with congenital stationary night blindness. In one of the 54 patients, only one eye had an abnormal ERG. The remaining two patients showed diffuse loss of the A wave and B wave in both eyes.

**Latency from diagnosis of primary to metastatic melanoma**

In 17 patients, the average time from malignant melanoma diagnosis to metastatic disease was 3.5 years (range, 2 months to 19 years) (Table 8). However, three patients (two UC Davis, one other institution) had no metastasis, and four patients (four UC Davis) were found to have metastatic disease but no history of primary cutaneous melanoma. Four patients (one UC Davis, three other institutions) presented with metastatic cutaneous melanoma.

### Latency from diagnosis of primary melanoma to MAR syndrome

In 32 patients, the time from the diagnosis of skin melanoma to diagnosis of MAR syndrome averaged 3.6 years (range, 2 months to 19 years) (Table 8). One patient (one other institution) presented with MAR syndrome first, then 2 weeks later was found to have a maxillary sinus malignant melanoma. Another patient (one other institution) also presented with MAR syndrome first, then 2 years later developed malignant melanoma.

### Latency from diagnosis of metastatic melanoma to MAR syndrome

In 13 patients, the elapsed time from diagnosis of metastatic disease to diagnosis of MAR syndrome averaged 1.9 years (range, 1 month to 15 years) (Table 8). MAR syndrome appeared within 1 year after recognition of metastasis in 10 patients (ten other institutions, not in averages because time of MAR presentation is unknown) (20). Five patients (three UC Davis, two other institutions) were found to have metastatic disease and MAR simultaneously. Two of the UC Davis patients had no history of primary melanoma. Six patients (four UC Davis, two other institutions) were discovered to have metastatic disease after the diagnosis of MAR, with an

---

**TABLE 2. Continued**

<table>
<thead>
<tr>
<th>Patient no./authors</th>
<th>Melanoma to metastasis (y)</th>
<th>Melanoma to MAR (y)</th>
<th>Melanoma to survival (y)</th>
<th>Melanoma treatment</th>
<th>Serum analyzed at UC Davis</th>
</tr>
</thead>
<tbody>
<tr>
<td>56/UC Davis patient 5</td>
<td>No metastasis</td>
<td>3</td>
<td>4</td>
<td>Surgery</td>
<td>YES</td>
</tr>
<tr>
<td>57/UC Davis patient 6</td>
<td>MAR presented first, 4 mo later. A left axillary lymph node metastasis melanoma was found. No primary cutaneous melanoma</td>
<td>4.3</td>
<td>Cytoreductive surgery</td>
<td>None</td>
<td>YES</td>
</tr>
<tr>
<td>58/UC Davis patient 7</td>
<td></td>
<td>3.3</td>
<td>4.5</td>
<td>Metastatic melanoma removal with cytoreductive surgery</td>
<td>Prednisone for 10 d → not improved. IVIg 200-220 g/mo x 9 → improved</td>
</tr>
<tr>
<td>59/UC Davis patient §§§</td>
<td>No metastasis</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>60/UC Davis patient §§§</td>
<td></td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>61/UC Davis patient</td>
<td></td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>1§§§</td>
<td></td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>62/UC Davis patient</td>
<td></td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

* Pollock, et al., Melanoma-associated retinopathy (MAR), presented as a poster at the NANOS meeting, 1992.

† Two cases reported. One of them had been reported previously by Alexander et al., 1992 (14).

‡ Twelve cases reported. Two of them had been reported previously by Alexander et al., 1992 (14) and Milam et al., 1993 (16).

§ One patient's clinical information was available through personal communication with Dr. Leah Levi, San Diego, California (Patient 27).

∥ One case reported. It had been reported previously by Rougier et al., 1995 (24).

¶ Three cases reported; two of them had been reported by Kim et al., 1994 (21) and Kellner et al., 1995 (23); one is new and without clinical information.

**TABLE 3. Available age and gender information**

<table>
<thead>
<tr>
<th></th>
<th>UC Davis patients (n = 24)</th>
<th>Patients from other institutions (n = 16)</th>
<th>Total (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age (range)</td>
<td>59.2 (30–78)</td>
<td>55.3 (30–78)</td>
<td>57.5 (30–78)</td>
</tr>
<tr>
<td>No. of men</td>
<td>18</td>
<td>15</td>
<td>33</td>
</tr>
<tr>
<td>No. of women</td>
<td>6</td>
<td>1</td>
<td>7</td>
</tr>
</tbody>
</table>
average latency of 6.8 months (range, 2 months to 15 years). Three patients (two UC Davis, one other institution) had no evidence of metastatic disease.

### Survival time after diagnosis of cutaneous melanoma

Survival time after diagnosis of cutaneous melanoma averaged 5.9 years (range, 1–19.5) (Table 9). Five patients from UC Davis died after 1, 2, 8 (two patients), and 19 years; six patients from other institutions died after 3, 4, and 5 years (four patients).

### Treatment of melanoma

Eighteen patients had treatment limited to excision of melanoma or metastatic disease. Nine patients are alive, and three patients have died (average lifespan, 6.9 years) from progression of metastatic disease. In six patients, there was no survival information. Six UC Davis patients and seven patients from other institutions had a variety of other treatments for the cutaneous melanoma, which included cytoreductive surgery, chemotherapy, radiation, and immunotherapy.

### Treatment of MAR syndrome

Treatment consisted of oral, subtenon’s, or intravenous corticosteroids, plasmapheresis, intravenous immunoglobulin (IVIg), azathioprine, gabapentin, and x-irradiation of metastases or cytoreductive surgery. Oral prednisone alone was not beneficial in six of seven patients treated; one patient (patient 1) had such dramatic improvement in Goldmann visual fields and ERG (patient 37). The combination of oral prednisone, plasmapheresis, azathioprine, and gabapentin helped one patient with slight improvement (10) (Table 10). Plasmapheresis alone was not beneficial in one patient (patient 11) (17). The combination of oral prednisone, plasmapheresis, azathioprine, and gabapentin helped one patient with slight improvement in Goldmann visual fields and ERG (patient 37). X-irradiation improved the vision of one patient when metastases shrank (patient 27).

IVIg treatment improved visual acuity in one patient (patient 55, see details that follow). The combination of intravenous methylprednisolone and plasmapheresis improved the visual acuity and field of one patient (patient 56, see details that follow). Cytoreductive surgery improved color vision and visual field in one patient (patient 52) two years after removal of the metastatic tumor (Dr. Rafael Caruso, National Eye Institute, personal communication) and visual acuity and field in another patient (patient 57, see details that follow). The combination of cytoreductive surgery and IVIg improved some aspects of visual function in two patients (patients 39 and 58, see details that follow) (Dr. Michael Vaphiades, Department of Ophthalmology and Neurology, University of Arkansas, personal communication regarding patient 39).

Clinical details of the following four newly reported patients (patients 55–58) illustrate the beneficial effect of treatment on visual function.

**Patient 55.** A 47-year-old man developed metastatic melanoma to bone, skin, lung, and brain 6 years after the initial diagnosis of a cutaneous malignant melanoma of the left leg. He developed MAR 1 year after the onset of metastasis. Treatment of metastatic melanoma consisted of chemotherapy with interferon, tamoxifen, and interleukin-2, as well as x-irradiation to brain, back, and neck. When seen at the University of California, Davis, Neuro-Ophthalmology Service on July 14, 1997, he had visual acuities of 20/20 +1 OU and constricted visual fields. However, on August 29, 1997, he complained of decreased visual acuity OS. Finger counting visual acuity was present OS with a new left relative afferent pupillary defect. He underwent treatment with IVIg (400 mg/kg per day for 5 days). When reexamined 4 days later, his OS visual acuity had improved to 20/200. By September 30, it had improved to 20/25 –2. However, he developed further metastatic disease and died in December 1997.

**Patient 56.** A 76-year-old woman underwent removal of a malignant melanoma from her right shoulder 3 years before developing MAR syndrome. There were no known metastases. Before the melanoma diagnosis, she had developed posterior ischemic optic neuropathy in the left eye. She developed MAR 1 year after the initial diagnosis of metastatic melanoma to the brain. She received treatment with chemotherapy with interferon and tamoxifen. Her OS visual acuity improved to 20/200. By September 30, it had improved to 20/25 –2. However, she developed further metastatic disease and died in December 1997.

### Table 4. Visual acuity

<table>
<thead>
<tr>
<th></th>
<th>UC Davis patients</th>
<th>Patients from other institutions</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual acuity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At presentation</td>
<td>≥20/60</td>
<td>&lt;20/60</td>
<td>≥20/60</td>
</tr>
<tr>
<td>Last recorded</td>
<td>13</td>
<td>3</td>
<td>13</td>
</tr>
</tbody>
</table>

### Table 5. Visual field abnormalities

<table>
<thead>
<tr>
<th>Visual field abnormalities</th>
<th>UC Davis patients (n = 17)</th>
<th>Patients from other institutions (n = 10)</th>
<th>Total (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall constriction</td>
<td>13</td>
<td>5</td>
<td>18</td>
</tr>
<tr>
<td>Central or paracentral scotoma or depression</td>
<td>11</td>
<td>7</td>
<td>18</td>
</tr>
<tr>
<td>Articulate defects</td>
<td>4</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>

### Table 6. Vitreoretinal abnormalities

<table>
<thead>
<tr>
<th>Vitreoretinal abnormalities</th>
<th>UC Davis patients (n = 18)</th>
<th>Patients from other institutions (n = 25)</th>
<th>Total (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>6</td>
<td>13</td>
<td>19</td>
</tr>
<tr>
<td>Optic disc pallor</td>
<td>9</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Retinal vessel attenuation</td>
<td>9</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>RPE changes</td>
<td>6</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Vitreous cells</td>
<td>5*</td>
<td>8</td>
<td>13*</td>
</tr>
<tr>
<td>ERM</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

*One patient also had a marked retinal periphlebitis (20). RPE: retinal pigment epithelium; ERM: epiretinal membranes.
neither eye was examined, with superior altitudinal visual field loss OU. Best-corrected visual acuities were 20/50 OU and visual fields were constricted. Over the subsequent 5 months, she developed severe visual field constriction and a reduction in visual acuity to 20/60 OD and 20/200 OS. She was treated with four courses of plasmapheresis and 125 mg intravenous methylprednisolone twice daily over a 10-day period. After the first plasmapheresis and 2 days of intravenous corticosteroid treatment, visual acuity had improved to 20/60 OU. After the third plasmapheresis treatment and 7 days of intravenous methylprednisolone, near vision had improved to Jaeger 2 in both eyes. Goldmann visual fields eventually expanded to baseline.

**Patient 57.** A 42-year-old man was examined on March 18, 1996, with a one-week complaint of shimmering and blurry vision OS and difficulty with night vision. Visual acuity was 20/20 OU, and the rest of the ophthalmic examination was normal. Over the next 10 days, he developed similar symptoms OD and more blurriness in his vision. On April 5, 1996, his visual acuity was 20/15 OD and 20/30 OS. A left relative afferent pupillary defect appeared. Computed tomography and magnetic resonance imaging of the head were normal. Mitochondrial genetic analysis for Leber's hereditary optic neuropathy and a fluorescein angiogram were normal. An ERG analysis showed extensive and progressive field loss in both eyes. On his initial visit to the University of California, Davis, Neuro-Ophthalmology Service on February 11, 1999, he had 20/20 visual acuity OU but visual field constriction. Humphrey visual field testing showed mean deviations of -28.85 dB OD and -27.72 dB OS (Fig. 2a). A PET scan showed a lump in his left axilla, which proved on resection to be a metastatic melanoma. From August 1999 to May 2000, he received a total of nine IVIg treatments, approximately 200 to 220 g each time. On September 20, 2000, Humphrey visual field testing showed improvement in visual field mean deviations to -13.00 dB OU (Fig. 2b).

**Pathology**

The eyes of one patient (patient 27), studied postmortem by conventional histopathologic techniques, showed no pathologic abnormalities.

**Electroretinographic abnormalities**

<table>
<thead>
<tr>
<th>Electroretinographic abnormalities</th>
<th>UC Davis patients (n = 20)</th>
<th>Patients from other institutions (n = 36)</th>
<th>Total (n = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSNB pattern</td>
<td>19</td>
<td>35*</td>
<td>54</td>
</tr>
<tr>
<td>Almost extinguished OU</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

* One of these patients had a normal ERG in the right eye and a CSNB type in the left eye. CSNB, congenital stationary night blindness.

**Survival after diagnosis of cutaneous melanoma**

<table>
<thead>
<tr>
<th></th>
<th>UC Davis patients</th>
<th>Patients from other institutions</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Living</td>
<td>n = 11</td>
<td>n = 1</td>
<td>n = 12</td>
</tr>
<tr>
<td>Died</td>
<td>n = 5</td>
<td>n = 6</td>
<td>n = 11</td>
</tr>
<tr>
<td>Average survival, y (range)</td>
<td>6.4 (1-19.5)</td>
<td>4.7 (3-5.7)</td>
<td>5.9 (1-19.5)</td>
</tr>
</tbody>
</table>
TABLE 10. Visual outcome with melanoma-associated retinopathy treatment

<table>
<thead>
<tr>
<th>Therapy performed</th>
<th>Patient no.*</th>
<th>Outcome</th>
<th>Patient no.*</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral prednisone (n = 7)</td>
<td>13</td>
<td>No improvement</td>
<td>5</td>
<td>No improvement</td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>No improvement</td>
<td>30</td>
<td>Decreased haze, but further visual deterioration†</td>
</tr>
<tr>
<td>Plasmapheresis (n = 1)</td>
<td>11</td>
<td>No improvement, progressive VF loss</td>
<td>10</td>
<td>VA not improved, but decreased haze and improved GMVF‡</td>
</tr>
<tr>
<td>Oral prednisone, plasmapheresis, azathioprine, gabapentin (n = 1)</td>
<td>37</td>
<td>Mild improvement in GMVF and ERG, but visual symptoms remained§</td>
<td>1</td>
<td>Dramatic improvement in VA§</td>
</tr>
<tr>
<td>Radiation therapy (n = 1)</td>
<td>27</td>
<td>Vision worsened with metastasis recurrence, improved after shrinkage of metastasis with radiation therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVlg alone (n = 1)</td>
<td>55</td>
<td>Improved in VA</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>IVMP and plasmapheresis (n = 1)</td>
<td>56</td>
<td>Improved in both VA and VF</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Cytoreductive surgery (n = 2)</td>
<td>52</td>
<td>Spontaneously improved in color vision and VF 2 y after removal of metastatic tumor</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>IVlg and cytoreductive surgery (n = 2)</td>
<td>57</td>
<td>Improved in both VA and VF</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td></td>
<td>58</td>
<td>Improved in color vision, GMVF, and visual symptoms</td>
<td>58</td>
<td></td>
</tr>
</tbody>
</table>

* Numbers refer to patient numbers on Tables 1 and 2.
† Improvement in cellular response but no change in visual function.
‡ Improvement in cellular response and GMVF but no change in VA.
§ VA improved from light perception OU to 20/50 OD, 6/200 OS. This result is atypical from all the other cases with oral prednisone treatment.

ERG, electroretinogram; GMVF, Goldmann visual field; IVlg, intravenous immunoglobulin; VA, visual acuity; VF, visual field; IVMP, intravenous methylprednisolone.

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Sections of the metastatic melanoma from patient 58 reacted with rabbit anti-whole bovine retina serum. Some of the cells that composed the various cell types of that melanoma reacted with the rabbit anti-whole bovine retina serum, indicating a possible source of his retinal sensitization (Fig. 4). This finding is presumptive evidence of retinal immune hypersensitivity in MAR syndrome.

**DISCUSSION**

The earliest report of a patient with MAR-like syndrome is credited to Gass in 1984 (10). The patient, who had profound visual loss together with a diagnosis of metastatic melanoma, was believed to have an acute Vogt-Koyanagi-Harada-like syndrome. Vision improved dramatically after steroid treatment, a response very different from subsequently reported MAR cases. The patient also had a prominent vitreous and anterior chamber cellular reaction, lymphocytic cerebrospinal fluid pleocytosis, and depigmentation of the retina and skin. These signs suggest a uveomeningitic syndrome rather than MAR syndrome.

Two more cases of patients with a MAR-like syndrome were described before the recognition of MAR as a distinct clinical entity. The first, reported by Ripps et al. (11) in 1984, was attributed to vincristine toxicity. The second, reported by DuBois et al. (12) in 1988, initially attributed night blindness to migraine. In 1991, the same authors reported in a letter (47) that the patient had developed cutaneous malignant melanoma 2 years after the onset of night blindness and acknowledged the similarities between their case and a case of MAR reported in 1988 by Berson and Lessell (13).

The seminal paper on MAR syndrome by Berson and Lessell (13) postulated a paraneoplastic cause of night blindness in a patient with malignant melanoma. Subsequently, Milam et al. (16) recognized that patients with MAR have circulating IgG autoantibodies showing specific immunofluorescent staining of some human rod bipolar cells. The bipolar cell antigens on which these antibodies react remain unknown; some evidence suggests that they are made of polar lipid (20).

MAR syndrome affects predominantly males, as seen in Table 3. The male:female ratio of 4.7:1 far exceeds the 5:4 incidence of malignant cutaneous melanoma in the United States (48).

MAR patients have been believed to retain near-normal visual acuity, color vision, and central visual field (1), but our review clearly shows that a minority loses central vision. Visual acuity may deteriorate later on, as seen in Table 4 and exemplified by patients 55 and 56. Visual fields have shown central and peripheral loss with progression (patients 57 and 58).

Visual symptoms include shimmering, flickering, or pulsating photopsias and difficulty with night vision. The ERG shows the typical features of a markedly reduced dark-adapted B wave and preservation of an A wave, resembling that seen in congenital stationary night blindness (1). Defects in the function of cone “on” center bipolar cells and blue-sensitive cones occur in some patients (14,16,23). There is evidence that the damage is restricted to cells of the magnocellular pathway (28). The “off,” or hyperpolarizing, bipolar cells seem to be spared (14,23). Other abnormal electrophysiologic findings reported in some MAR patients are reduced A wave amplitude in the photopic or scotopic ERG (19,35), reduced amplitudes of the photopic ERG (14,19,23,24), reduced amplitudes of oscillatory potentials (14,16,19,21), maximum stimulus intensity amplitude reduction (23), abnormalities in the 30-Hz flicker-response latency (16,19,26,33) or amplitude (19,23), and an abnormal pattern ERG (38).

In this study, two patients showed an almost extinguished ERG pattern with diffuse loss of both A and B waves, and one patient had an abnormal ERG in only one eye (Table 7).

MAR syndrome is generally believed to occur only after patients have developed metastatic melanoma (20), but our review disclosed two patients who presented with MAR before the diagnosis of a primary melanoma, three who had no evidence of metastatic disease, five patients who presented with a simultaneous diagnosis of metastatic cutaneous melanoma and MAR, and six whose...
metastasis was diagnosed after the onset of MAR. In addition, one case of MAR-like syndrome was described in a patient with anti-retinal bipolar cell antibodies with no cutaneous melanoma after 4 years of follow-up (49).

The immunologic and electrophysiologic abnormalities in patients with MAR syndrome suggest that the underlying pathogenic mechanism is molecular mimicry, such as has been described in other paraneoplastic syndromes (50). According to this mechanism, MAR syndrome occurs when susceptible individuals produce an immune response that cross-reacts with retinal rod bipolar cells, with which the melanoma cells share antigenic...
epitopes. Neuretinal transmission from the photoreceptors through the inner retina is then disrupted (16, 20). Our finding that the metastatic melanoma removed from patient 58 expressed antigens that react with rabbit anti-whole bovine retina antibodies supports the proposal of molecular mimicry as the underlying pathogenic mechanism in MAR syndrome (Fig. 4).

Immunologic heterogeneity is recognized in MAR. Involvement of "on" bipolar cells has been implicated (14, 20, 34). We previously reported that patient 13 had an autoreactivity reaction with a 22-kd neuronal antigen found in the retina but not in the optic nerve (43). Other studies suggested that a novel membrane-associated 33-kd protein and a 35-kd retinal Müller cell protein could be the MAR antigens (37, 51). In our study, the variety of retinal antigens involved in indirect immunohistochemical staining (Fig. 3b and c) and Western blot analysis strongly suggests that several antigens, shared by the retina and the neoplasm, may be involved. In addition, anti-bipolar cell antibodies have been demonstrated in a patient with CAR syndrome from adenocarcinoma of the colon (52).

Although our patients' sera specifically recognized retinal bipolar cells with indirect immunohistochemistry, we were unable to identify MAR-specific retinal antigens by Western blot technique. It has been postulated that the absence of specific staining by MAR sera on Western blots could be due to modification of amino groups by paraformaldehyde, denaturation by sodium dodecyl sulfate, and obscuration of MAR-specific antigen by a nonspecifically stained component (16). It is possible that the MAR-specific retinal antigens may not be proteins, but gangliosides, proteoglycans (16), lipids (20), carbohydrates, or a combination of these substances.

Milam et al. (16) reported that sera from MAR patients and some normal subjects produced nonspecific background labeling of all parts of the human retina and specific staining of nerve fiber layer. A pattern of diffuse staining of human MAR IgG throughout the retina in rhesus monkey eyes was recently reported (34). We found that the analysis of MAR sera by indirect immunohistochemistry on sectioned rhesus monkey eyes disclosed diffuse antibody involvement with optic nerve, retinal nerve fiber layer, and photoreceptors as well as bipolar cells (Fig. 3). Notably, more than half of the UC Davis patients showed optic disc pallor (Table 6). The staining of nerve fiber layer, optic nerve, and ganglion cells may be related to damaged neurotransmission or merely a harmless epiphenomenon.

Histopathologic studies of postmortem retinas from MAR patients have been previously reported (22, 32). In the first case, Okel et al. (22) found considerable loss of macular anatomy, with marked degeneration of photoreceptor cells and extensive destruction of the neurosensory retina beyond the bipolar layer. In the second case, Gritinger and Smith (32) observed marked reduction in the density of bipolar neurons in the inner nuclear layer. Photoreceptor cell neurons in the outer nuclear layer were normal. Ganglion cells were present, although many showed evidence of transsynaptic atrophy. These anatomic changes are consistent with the clinical, immunologic, and electrophysiologic data that implicate the bipolar cells as the primary site in MAR syndrome. In contrast, in patient 27, from whom eyes were made available in our study, histopathologic examination revealed no apparent anatomic abnormalities by light microscopy, even though indirect immunohistochemistry showed strong antibody activity on nerve fiber layer, inner nuclear layer, outer plexiform layer, outer nuclear layer, outer segment of photoreceptor cells, and the retinal pigment epithelium (Fig. 3). Thus, the three cases of histopathology discussed above (two previously reported cases and the current study) showed the diverse findings of normal retinal structure to widely destroyed retinal structure.

Treatment of the visual loss of MAR has been largely ineffective. However, occasionally combinations of cytoreductive surgery, x-irradiation, intravenous corticosteroids, plasma exchange, and IVIg have shown some benefit.

IVIg has been shown to be efficacious in the treatment of two of three patients with paraneoplastic visual loss associated with CAR syndrome (53). It has been useful in other autoimmune neurologic diseases, including Guillain-Barré syndrome, myasthenia gravis, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, multiple sclerosis, dermatomyositis (54–57), and in other immunologic ophthalmologic conditions, such as ocular cicatricial pemphigoid (58), refractory uveitis (59), and linear IgA bullous disease limited to the eye (60).

All preparations of IVIg are comparable in safety, efficacy, and cost. Although the different pools of human donors used by the various manufacturers contain a wide range of anti-idiotypic antibody specificities, there are no documented differences in the efficacy of certain products or lots for a given patient or a specific disease. The empirical therapeutic dose of IVIg is 2 g/kg. Whereas the past practice has been to divide the total dose for infusion into five daily doses of 400 mg/kg each, the current recommendation is to divide the total dose into two daily doses of 1 g/kg each. The rate of infusion should not exceed 200 mL/h or 0.08 mL/kg per minute. Because of the drug's rapid diffusion to the extravascular space, achieving a high concentration of IVIg within 2 days may enhance its efficacy (54, 61).

There is concern that immunomodulatory therapy such as IVIg, although decreasing the titer of circulating autoantibodies, may increase the cancer mortality because MAR patients may have antibodies that are protective against tumor spread. However, in the patients whom we studied, there is no difference in survival between MAR patients, treated or untreated, and those without MAR. There are experimental studies that show the efficacy of IVIg as an antitumor agent (62–64).

Current research suggests that cytoreductive surgery (complete metastasectomy) and adjuvant immunotherapy...
should be the initial treatment of most patients with melanoma metastatic to distant sites since 90% of such patients have only one to three metastatic sites detectable with modern scanning technology (65). Adjuvant immunotherapy can be used after the induction of a complete clinical remission by cytoreductive surgery (65). In a recent case of CAR syndrome secondary to adenocarcinoma of the colon with retinal anti-bipolar cell antibodies, several months after resection of the tumor and chemotherapy, there was no evidence of cancer or anti-bipolar cell antibodies, and the ERG and visual fields were markedly improved. Thus, effective treatment of cancer may result in elimination of associated anti-retinal antibodies and improved retinal function (52).

Cancer cells, including those of malignant melanoma, generate factors that facilitate tumor growth by suppressing the immune system (66–69). The degree of general immunosuppression correlates with the total burden of melanoma cells in the body (70). Melanoma cells also express multiple melanoma-associated antigens that may induce the production of circulating autoantibodies or other factors that block the ability of lymphocytes to kill melanoma cells (71), or activate T cells to suppress the anti-tumor response (67). These autoantibodies may cross-react with retinal rod bipolar cells in susceptible hosts, resulting in MAR syndrome. Therefore, by removing most of the immunogenic activities of melanoma cells and decreasing the tumor burden, cytoreductive surgery not only facilitates the resolution of MAR but also allows the recovery of the host’s anti-tumor immune response. Among the seven MAR patients who experienced visual improvement, four (patients 39, 52, 57, and 58) had cytoreductive surgery. Patients 52 and 57 improved with cytoreductive surgery alone, whereas patients 39 and 58 received cytoreductive surgery in addition to IVIg. The importance of decreasing the melanoma tumor burden in the treatment of MAR syndrome is further demonstrated by the clinical course of patient 27. This individual experienced a worsening of visual acuity every time the metastasis recurred, and improvement in visual acuity when the metastatic disease was reduced with radiation therapy. In MAR, as well as other central nervous system paraneoplastic syndromes, other therapies have been generally less effective than cytoreductive surgery and IVIg (3,9,72–78).

Results of a randomized trial in the adjuvant treatment of metastatic malignant melanoma have shown promise. Patients receiving adjuvant immunotherapies such as CancerVax/bacille Calmette-Guerin (BCG) and GM2 ganglioside/BCG vaccine had prolonged disease-free intervals and increased survival rate compared with those who received BCG alone (79). Vaccination with treated autologous cells has been attempted (80). Dendritic cell-based vaccine and gene therapy have also been promising (81–84). Another emerging therapy involves the transfection of cutaneous malignant melanoma nodules with retrovirus-mediated herpes simplex type 1 thymidine kinase suicide genes, rendering the transfected cells susceptible to ganciclovir. In another study, autologous tumor cells transfected with interleukin-2 genes were injected back into patients to generate an immune response (85). Yet another approach involves injection of vaccinia/GM–cerebrospinal fluid constructs directly into subcutaneous metastases (86).

The treatment of patients with malignant melanoma and MAR syndrome should be directed at decreasing the tumor burden, with resection of visible metastatic tumor masses by cytoreductive surgery so that any adjuvant immunotherapy can become more effective. Other medical treatments are reserved for patients whose ophthalmic manifestations are not relieved by these approaches.

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This paper is dedicated to Ronald M. Burde, MD.

ADDENDUM

Since our manuscript was submitted for publication, we are aware of two additional cases of melanoma-associated retinopathy with unusual fundus findings. Case 1 was a 47-year old female with MAR syndrome with round and oval, white lesions that involved the outer retinal pigment epithelium. The lesions affected the macula, reducing the patient’s visual acuity. Case 2 was a 57-year old male with MAR syndrome with diffuse retinal pigment epithelial loss of pigment and numerous small, atrophic lesions which involved the retinal pigment epithelium and choroid. This patient also developed...
vitiligo. Both patients had antibodies reactive against retinal bipolar cells. These fundus lesions are unusual for MAR syndrome.

Thus, the total number of melanoma-associated retinopathy patients reported to date is 64.


REFERENCES


Original Contribution

Evaluation of Transdermal Scopolamine as Treatment for Acquired Nystagmus

Jae-II Kim, MD, PhD, Lea Averbuch-Heller, MD, and R. J. Leigh, MD

We conducted an unmasked evaluation of transdermal scopolamine in seven patients with acquired nystagmus for whom other treatments had been unsatisfactory. We measured eye speed and visual acuity before and several hours after starting treatment. Median eye speed decreased slightly in three patients but increased in two; no change in visual acuity occurred in any patient. One patient was unable to tolerate the side effects of scopolamine after two hours, but the others continued the scopolamine treatment for 48 hours; only one reported minor improvement. We conclude that transdermal scopolamine is not likely to be an effective treatment of acquired nystagmus. Patients should be monitored during the first few hours of treatment to determine whether vision is improved or made worse and whether side effects occur.

Key Words: Nystagmus—Scopolamine—Gabapentin—Eye movements.

A prerequisite for clear vision is that images of the world be held steadily on the retina. Acquired forms of nystagmus cause excessive motion of retinal images, which often degrades vision and causes oscillopsia—illusory motion of the seen world (1). At present, several drug treatments may alleviate specific types of nystagmus. Thus, baclofen is often effective therapy for periodic alternating nystagmus (2) and acetazolamide suppresses the nystagmus associated with familial episodic vertigo and ataxia type 2 (3). Patients with acquired pendular nystagmus, in association with multiple sclerosis or as a component of oculopalatal tremor, may benefit from either gabapentin (4), or memantine (5). Some patients with upbeat or downbeat nystagmus benefit from baclofen (6) or clonazepam (7). However, not all patients are helped or able to tolerate these agents. For example, a side effect of gabapentin is that it may make ataxia worse. Thus, there is a need to identify and evaluate new potential treatments for nystagmus and its visual consequences (8).

Basic studies using the technique of pharmacologic inactivation have presented evidence that the neurotransmitters gamma-aminobutyric acid (GABA) and glutamate play an important role in the normal mechanism by which gaze is held steady during visual fixation (9,10), and which depends on structures in the rostral medulla (nucleus prepositus hypoglossi, medial vestibular nucleus), and their cerebellar connections. In addition, both muscarinic and nicotinic receptors have been demonstrated in the medial vestibular nucleus (11). Previous trials of drugs with cholinergic effects in patients with acquired nystagmus produced mixed results. A double-blind evaluation of trihexyphenidyl showed little benefit and concluded that the side effects outweighed the benefits of the drug in most patients (12). However, intravenous scopolamine (hyoscine) has been reported to suppress both pendular nystagmus and downbeat nystagmus (13,14). Scopolamine can also be administered transdermally and has been reported to help occasional patients with pendular nystagmus associated with multiple sclerosis (5). We studied seven patients with various forms of acquired nystagmus, making precise measurements of the oscillations before and during scopolamine therapy. Our goal was to determine whether transdermal scopolamine improved vision and suppressed nystagmus in this group of patients for whom other treatments had proved unsatisfactory.
TREATMENT OF NYSTAGMUS

### METHODS

We studied seven patients with acquired nystagmus, all of whom complained of oscillopsia that interfered with daily activities such as reading. The features of their illness, characteristics of their nystagmus, current medications, and prior treatments for nystagmus are summarized in Table 1. All patients had been tried on a variety of other drugs, including gabapentin, but either these drugs were ineffective or produced undesirable side effects. None had glaucoma or general medical disorders that would be a contraindication to administering scopolamine. All patients gave informed consent in accordance with our Institutional Review Board and the tenets of the Declaration of Helsinki.

Before starting treatment, we performed a general neuro-ophthalmologic examination and measured eye movements using the magnetic search coil technique, as previously described (4). In Patient 2, who had filamentary keratitis, we used an infrared video eye movement monitor. We were able to measure movements of both eyes before and during scopolamine in Patients 1 and 2, and the eye with the greater nystagmus in the other patients. Measurements of visual acuity were summarized in Table 1. Patients were also asked to view a light-emitting diode in a dark room to characterize their oscillopsia.

We tested fixation (small target at 1.2 or 15 cm), saccades, smooth pursuit, and the vestibulo-ocular reflex, as previously described (4). Eye position signals were digitized at 200 Hz and differentiated. For pendular nystagmus, saccades were removed interactively and the first 10 seconds of these records of nystagmus velocity (array size, 2,000 points) were then converted to eye speed (absolute value of velocity measurements) and the median value was computed. We also measured the predominant frequency of pendular oscillations, using a fast-Fourier transform. For jerk nystagmus waveforms, we interactively measured slow-phase velocity. We compared the eye speed of each directional component of nystagmus during similar fixation conditions from corresponding eyes before and after each treatment using the Wilcoxon signed-rank test (because some of the data were not normal in distribution). In the case of Patient 5, who had divergent nystagmus (convergent slow phases), we compared the eye speed during epochs when the measured convergence angle (during far or near viewing) was similar (27-31 degrees), before and during treatment.

After making these baseline measurements, a 1.5-mg scopolamine patch (Transderm Scop; Novartis, East Hanover, NJ) was applied to an area of skin behind one ear, as recommended by the manufacturer. Patients were subsequently monitored for any side effects, such as confusion or unsteadiness. Measurements of visual function and eye movements were repeated after approximately four hours (range, 2-5.5). We repeated measurements in Patient 1 after only two hours because she reported systemic effects and wanted to end the session. All except Patient 1 continued to wear the patch for another two days and then reported whether there had been any subjective improvement of their symptoms.

### RESULTS

No patient showed any change—improvement or deterioration—of visual acuity after wearing the scopolamine treatment for approximately four hours. Patients 1, 2, and 6 reported modest improvement of their oscillopsia. Comparisons of the effects of scopolamine on each

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### TABLE 1. Summary of clinical findings in patients studied

<table>
<thead>
<tr>
<th>No./age/gender/diagnosis/duration*</th>
<th>Visual acuity</th>
<th>Drug</th>
<th>Nystagmus features†</th>
<th>Effects of other treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R: 0.29; L: 0.09;</td>
<td>Alprazolam</td>
<td>4.5 Hz pendular; right- and left- superiority</td>
<td>Gabapentin: reduced nystagmus; worsened ataxia; Trihexyphenidyl: minor effects</td>
</tr>
<tr>
<td></td>
<td>bilateral OP R&gt;L</td>
<td></td>
<td>CW-beating; H &gt; V &gt; T; R-L</td>
<td></td>
</tr>
<tr>
<td>P2/37/M/OPT/2</td>
<td>R: 0.4; L: 0.8;</td>
<td>Verapamil</td>
<td>2 Hz pendular; V &gt; H; R &gt; L</td>
<td>Gabapentin: reduced nystagmus; worsened ataxia</td>
</tr>
<tr>
<td></td>
<td>normal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P3/47/F/MS/3</td>
<td>R: 0.67; L: 0.9;</td>
<td>Lorazepam</td>
<td>Upright with divergent horizontal component</td>
<td>Gabapentin, trihexyphenidyl, clonazepam: minor effects</td>
</tr>
<tr>
<td></td>
<td>normal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P4/49/F/RML/9</td>
<td>R: 0.8; L: 0.8;</td>
<td>Amitriptyline</td>
<td>Torsional; CW-beating, with downbeat component; R-L</td>
<td>Gabapentin, clonazepam, amantadine, lamotrigine, niurol, baclofen: minor effects</td>
</tr>
<tr>
<td></td>
<td>normal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P5/41/M/Chiari/4</td>
<td>R: 1.0; L: 1.0;</td>
<td>Transyl-cypromine</td>
<td>Divergent-beating horizontal</td>
<td>Gabapentin, clonazepam, baclofen: minor effects</td>
</tr>
<tr>
<td></td>
<td>normal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P6/55/M/OPT/4</td>
<td>R: 0.5; L: 0.67;</td>
<td>None</td>
<td>1.5 Hz pendular; V &gt; T &gt; H; R-L</td>
<td>Gabapentin, clonazepam: minor effects</td>
</tr>
<tr>
<td></td>
<td>normal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P7/42/F/MS/11</td>
<td>R: 0.1; L: 0.29;</td>
<td>Fluoxetine</td>
<td>3.0 Hz pendular; R-L; H&gt;V</td>
<td>Gabapentin, clonazepam: minor effects</td>
</tr>
<tr>
<td></td>
<td>bilateral OP R&gt;L</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Age and duration are in years.
† Visual acuity is expressed as decimal values. Bilateral indicates bilateral evidence of demyelination and worst affected eye (e.g., R > L: right worse than left), as judged by optic disc pallor (OP), color vision, or relative afferent pupillary responses to light.
‡ Predominant frequency of pendular component, presence of any jerk or other superimposed waveform (CW, clockwise); relative amplitudes of horizontal (H), vertical (V), and torsional (T) components.

Chiari, Chiari malformation; MS, multiple sclerosis; OPT, oculopatatal tremor after brainstem stroke; RML, right medial lesion, undetermined (possible arteriovenous malformation).
directional component of nystagmus in each patient are summarized in Fig. 1. Eye speed showed small but significant \( (p < 0.01) \) decreases in Patients 1, 4, and 6. Patients 5 and 7 both showed significant \( (p < 0.01) \) increases of eye speed. For Patient 5, the increase in his divergent-beating nystagmus mainly occurred during near viewing. In Patient 7, the increase in median horizontal and vertical eye speed was greater than 70%; representative records are shown in Fig. 2. No changes in the predominant frequency of any of the cases of pendular nystagmus were noted.

Side effects from the scopolamine were noted by four patients at the time of the second recording, including mild dizziness (Patient 2), blurring of vision (Patient 3), change in balance (Patient 6), and a feeling “similar to having a glass of wine” (Patient 1). Patient 1 preferred not to continue wearing the scopolamine patch. Of the patients who continued the scopolamine treatment for another 48 hours, only Patient 6 reported modest benefits consisting of reduced oscillopsia and improved balance for the first few weeks. However, after wearing a scopolamine patch each weekend for approximately three months, the effect decreased, and he has stopped using it.

**DISCUSSION**

Transdermal scopolamine had inconsistent effects on the nystagmus in our patients, including modest decreases or increases of eye speed. Modest decreases are consistent with a previous study of pendular nystagmus in multiple sclerosis (5) but contrast with the substantial effects that intravenous scopolamine is reported to have in suppressing acquired pendular or downbeat nystagmus (13,14). The increase in eye speed was unexpected and not clearly related to the underlying disorder. Thus, Patients 1 and 7, both of whom had acquired pendular nystagmus in association with multiple sclerosis, showed a decrease of approximately 15% and increase of approximately 70% in eye speed, respectively. Nystagmus also increased in Patient 5 during convergence (increased speed of converging slow phases) when he was taking scopolamine. How can these disparate results be explained?

Scopolamine is a nonspecific antagonist of muscarinic receptors in the central nervous system (15). Acetylcholine plays only an efferent role in the peripheral vestibular system (16), but both muscarinic and nicotinic receptors have been demonstrated in the medial vestibular nucleus (11), which contributes to the gaze-holding network (9,10). Thus, it seems possible that scopolamine might be acting at the level of the gaze-holding mechanism (brainstem neural integrator), for which the medial vestibular nucleus is an important component. Microinjection of the GABA-ergic agents muscimol and bicuculline may produce either a deficient or unstable integration of ocular motor signals (9,10), depending on which part of the network of neurons in the rostral medulla is inactivated. In analogy, therefore, it seems possible that scopolamine by transdermal administration might produce different effects, depending on absorption and pathology affecting the gaze-holding mechanism. Much larger doses of scopolamine (owing to intrave-
nously administration) are effective in suppressing ny­
tagmus (13,14), but side effects make this mode of treat­
ment unfeasible. Indeed, scopolamine is known to
produce a variety of side effects on the nervous system,
especially confusion in patients with neurologic disease
(17). In general, our patients tolerated scopolamine well
apart from Patient 1, who after two hours, found the
effects on her sensorium undesirable.

Intravenous scopolamine is also reported to suppress
downbeat nystagmus (14); conversely, intravenous ad­
ministration of the acetylcholinesterase inhibitor physo­
stigmine worsens such nystagmus (6). None of our patients
had downbeat nystagmus, but it was recently demon­
strated that transdermal scopolamine has little effect on
the ‘‘chin-beating’’ nystagmus that normal subjects de­
velop when they are placed in an upside-down position
in darkness (18). Based on the results from our Patient 5,
it seems possible that scopolamine may have effects on
vergence mechanisms (increased gain), but more studies
are required to confirm this.

In conclusion, scopolamine by the transdermal route is
not likely to be an effective treatment, including patients
who are unresponsive to or unable to tolerate gabapentin.
Although we only compared effects of scopolamine on
eye speed during one session, none of our patients who
wore the scopolamine patch for several days thought that
it was a worthwhile treatment. Patients with neurologic disease who desire a treatment trial should be monitored during the first few hours that they take the medication to check whether the drug makes their nystagmus better or worse or causes undesirable side effects.

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REFERENCES

Optic Neuropathy and Chiasmopathy in the Diagnosis of Systemic Lupus Erythematosus

R. Michael Siatkowski, MD, Ingrid U. Scott, MD, Alan M. Verm, MD, Ann A. Warn, MD, Bradley K. Farris, MD, Mitchell B. Strominger, MD, and Evelyn M. L. Sklar, MD

Purpose: To report the clinical presentation of acute visual loss in six patients who were ultimately diagnosed with systemic lupus erythematosus (SLE).

Methods: Retrospective case series.

Results: All patients had a positive antinuclear antibody and elevated anti-double stranded DNA titers. Five of six patients demonstrated gadolinium enhancement of the optic nerve and/or chiasm on magnetic resonance imaging (MRI). Most patients showed initial improvement after treatment with high-dose systemic corticosteroids, but five experienced recurrences during steroid taper, requiring further treatment with immunosuppressive or cytotoxic medications.

Conclusions: Visual loss owing to optic neuropathy or chiasmopathy may be the presenting sign of SLE or the event that leads to this diagnosis. Gadolinium-enhanced MRI is useful for identifying anterior visual pathway lesions in these patients. Corticosteroids are effective in the treatment of this condition; however, relapses requiring further treatment are common.

Key Words: Optic neuropathy—Optic chiasm—Systemic lupus erythematosus—Vision loss.

Ophthalmologic and central nervous system (CNS) manifestations occur in 20 to 40% of patients with SLE (1-3). Involvement of the optic nerve or chiasm occurs in only 1% of patients with systemic lupus erythematosus (SLE), typically after the diagnosis has been established and multiple other manifestations are present (1,2,4). Optic neuropathy or chiasmopathy is rarely a presenting sign of SLE or the event that leads to this diagnosis (4,5). Two reports of magnetic resonance imaging (MRI) in SLE-related optic neuropathy do not identify any anterior visual pathway abnormalities (6,7), although another found enhancing optic nerve lesions in three of six patients with known SLE (8). We report six patients with rapid visual loss owing to anterior visual pathway disease who were ultimately diagnosed with SLE.

METHODS

After appropriate Institutional Review Board approval, patient charts were retrospectively reviewed and historical and clinical data extracted. Six patients from either the Dean A. McGee Eye Institute or the Bascom Palmer Eye Institute were identified.

RESULTS

Pertinent details are summarized in Table 1. Following are more detailed case reports to demonstrate the events that led to the diagnosis of SLE in these patients.

CASE 1

A 55-year-old man developed progressive loss of vision OS over 9 days. It was accompanied by periocular pain exacerbated by eye movements. Two years earlier, he had experienced an acute loss of vision OD to the no light perception (NLP) level. Workup at that time consisted of a normal complete blood count (CBC) and MRI of the brain, which revealed numerous periventricular white matter lesions. He was diagnosed with multiple sclerosis (MS), and observation was recommended. Visual (VA) acuity OD remained NLP.

On examination, VA was NLP OD and counting fingers (CF) OS, with only a small nasal field remaining.
The right optic disk was diffusely pale. The left disk was normal. MRI of the brain and orbits revealed enhancement of the left intracranial optic nerve, chiasm, and tract (Fig. 1). CBC was notable for lymphopenia [536 cells/mm$^3$ (normal, >1,500/mm$^3$)]. Antinuclear antibody (ANA) titer was positive at a dilution of 1:80, and anti–double-stranded DNA (dsDNA) antibody titer was 19.3 U/mL (normal, ≤1.0 U/mL). Anti-cardiolipin antibody titer was normal. Review of systems was notable for arthralgias in both knees and wrists.

A diagnosis of SLE was made, and 250 mg intravenous methylprednisolone every 6 hours was administered for 5 days followed by an oral prednisone taper. VA OS returned to 20/25 over 8 weeks, at which time the patient was on 20 mg prednisone daily. Prednisone was tapered over the following 10 weeks. Twelve days after completing the taper, VA OS deteriorated to 20/200 but returned to 20/200 1 week after reinstitution of 80 mg prednisone daily. Prednisone was tapered over 6 weeks, but 3 weeks later VA OS again deteriorated to 20/70. Despite reinstitution of 80 mg prednisone daily, VA OS declined to CF. Repeat anti–dsDNA antibody titer was still elevated, but had fallen to 7.0 U/mL. After another course of intravenous methylprednisolone, VA OS improved to 20/100. VA OD remained NLP. The patient was discharged on oral prednisone but was noncompliant and temporarily lost to follow-up. He returned 1 year later, with examination unchanged.

**CASE 2**

A 51-year-old woman presented with a 3-day history of progressive visual loss OS, with periorbital pain not exacerbated by eye movement. MRI findings revealed the onset of multiple arthralgias several months after the first episode of visual loss.

**TABLE 1. Summary of clinical and MRI findings**

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
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<tbody>
<tr>
<td>No. of relapses</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Final VA</td>
<td>NLP, 20/100</td>
<td>NLP, 20/200</td>
<td>NLP, 20/100</td>
<td>NLP, 20/200</td>
<td>NLP, 20/100</td>
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<tr>
<td>ANA</td>
<td>1:80</td>
<td>1:80</td>
<td>1:80</td>
<td>1:80</td>
<td>1:80</td>
<td>1:80</td>
</tr>
<tr>
<td>Anti-ds DNA</td>
<td>19.3</td>
<td>24.1</td>
<td>5.7</td>
<td>9.0</td>
<td>12.1</td>
<td></td>
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<tr>
<td>MRI findings</td>
<td>Left ON, C enhance, WML</td>
<td>Old parietal CVA</td>
<td>Bilateral ON, C enhance, WML</td>
<td>Bilateral ON, C enhance, WML</td>
<td>Bilateral ON, C enhance, WML</td>
<td>C enhance, WML</td>
</tr>
</tbody>
</table>

VA, visual acuity; NLP, no light perception; CF, count fingers; ON, optic nerve; ANA, antinuclear antibody titer; anti-dsDNA, anti–double-stranded DNA antibody titer in U/mL; RPR, rapid plasma reagin; Ab, antibody; MRI, magnetic resonance imaging; SLE, systemic lupus erythematosus; C, chiasm; T, optic tract; WML, white matter lesions; CVA, cerebrovascular accident

A diagnosis of SLE was established. Intravenous methylprednisolone 250 mg every 6 hours was administered for 5 days followed by an oral prednisone taper over 6 weeks. Examination after the patient completed the prednisone taper demonstrated a VA of 20/20 OD and 20/25 OS.

Eight weeks later, VA deteriorated acutely to NLP OD and 20/200 OS. Both optic disks demonstrated mild pallor. Intravenous methylprednisolone was reinstituted, with improvement in VA to 20/70 OD; VA OS remained at 20/200. Three months later, on a dose of 10 mg prednisone daily, the patient developed deterioration of VA to CF OD and OS, along with a transverse myelitis at the fourth thoracic level. After 5 days of intravenous methylprednisolone, VA returned to 20/400 OD and 20/200 OS. Six months later, VA was unchanged and the patient remained on prednisone 10 mg daily.
FIG. 1. Patient 1: T1-weighted axial MRI shows gadolinium enhancement of the left optic nerve (A), chiasm (B), and left optic tract (C) (arrows).

CASE 3
A 32-year-old woman developed progressive visual loss OD over 7 days, associated with periocular pain made worse by eye movement. Medical history was remarkable for 3 months of arthralgias involving wrists, knees, and ankles at age 19. Ocular examination revealed VA of LP OD and 20/15 OS. The right disk was slightly swollen and the left disk appeared normal. VA OD improved to hand motions over 1 week after injection of 40 mg triamcinolone acetonide into the sub-Tenon’s space. Over the next several weeks, VA OD improved to CF.

Two months later, the patient developed bilateral eye pain. VA remained CF OD but had decreased to LP OS. After receiving 250 mg intravenous methylprednisolone every 6 hours for 3 days, VA improved to 2/400 OD and 20/40 OS. During oral prednisone taper at a dose of 30 mg/d, VA OS deteriorated to 20/80. With reinstitution of another 3-day course of intravenous steroids, VA OS improved to 20/30 and remained 2/400 OD. Chronic steroid or immunosuppressive treatment was recommended, but the patient refused because of a desire to become pregnant.

Four months later, VA deteriorated to CF OU. Both optic disks were pale. MRI revealed enlargement and gadolinium enhancement of both optic nerves and chiasm (Fig. 2). ANA titer was positive at a dilution of 1:640 and anti-dsDNA antibody titer was 2.1 U/mL. Anticardiolipin antibodies were 24 MPL/mL (normal, <10 MPL/mL) and rapid plasma reagin (RPR) was positive at 1:16 dilution.

Diagnosis of SLE was made. The patient was treated again with intravenous methylprednisolone, followed by monthly cyclophosphamide. VA at last follow-up 7 months later was 5/200 OD and 20/200 OS. The patient later discontinued the cyclophosphamide and became pregnant. She developed facial changes that were originally interpreted by her obstetrician as chloasma but that

FIG. 2. Patient 3: T1-weighted coronal image reveals notable enlargement of the optic chiasm (arrow).
were thought by the rheumatologist to be typical of a malar rash.

**CASE 4**

A 42-year-old woman developed sudden visual loss OD 2 days before presentation. It was accompanied by a diffuse periocular pain not worsened by ocular movement. VA was 2/200 OD and 20/25 OS, and both optic disks appeared normal. MRI with gadolinium revealed enhancement of both optic nerves with multiple foci of increased signal in the cerebral white matter. The patient was presumed to have idiopathic optic neuritis and observation was recommended. Six days after presentation, VA declined to 1/200 OD and 20/40 OS. CBC was notable for leukopenia (2,300/mm$^3$) and lymphopenia (805/mm$^3$). ANA titer was positive to 1:620 and anti-dsDNA antibody titer was 5.7 U/mL.

Diagnosis of SLE was made, and the patient was treated with 250 mg intravenous methylprednisolone every 6 hours for 5 days followed by oral prednisone with a slow taper over 3 months, followed by therapy with azathioprine. VA improved to 20/25 OU. The patient also developed recurrent bouts of psychosis and depression.

One month after the steroids were tapered, the patient developed recurrent vision loss to 8/200 OD and 20/30 OS. She was again treated with 250 mg intravenous methylprednisolone every 6 hours for 5 days with no improvement in vision. MRI revealed gadolinium enhancement of both optic nerves and the chiasm (Fig. 3). ANA titer was positive at 1:160, and anti-dsDNA titer was elevated at 9.0 U/mL. Urinalysis showed 2+ proteinuria. Lumbar puncture showed a normal opening pressure with no cells, and normal protein and glucose. Further review of systems yielded the presence of upper extremity arthralgias for several months, establishing the diagnosis of SLE. During oral prednisone taper, VA OS deteriorated to CF OS. At last examination, on chronic low dose daily prednisone, VA OS was 5/225; VA OD remained NLP.

**CASE 5**

A 38-year-old woman experienced painless progressive loss of vision OD over 2 days to the NLP level. She was diagnosed with idiopathic optic neuritis and observation was recommended. Six weeks later, she noted visual loss OS. On examination at the neurologist’s office, VA was NLP OD and 20/80 OS. Computed tomography of the brain and orbits was normal. She was treated with 250 mg intravenous methylprednisolone every 6 hours for 5 days with no improvement in vision. MRI revealed gadolinium enhancement of both optic nerves and the chiasm (Fig. 3). ANA titer was positive at 1:160, and anti-dsDNA titer was elevated at 9.0 U/mL. Urinalysis showed 2+ proteinuria. Lumbar puncture showed a normal opening pressure with no cells, and normal protein and glucose. Further review of systems yielded the presence of upper extremity arthralgias for several months, establishing the diagnosis of SLE. During oral prednisone taper, VA OS deteriorated to CF OS. At last examination, on chronic low dose daily prednisone, VA OS was 5/225; VA OD remained NLP.

**CASE 6**

A 66-year-old woman had painless, progressive visual loss bilaterally for 1 week. There was also a 2-year history of fatigue and arthralgias, and an episode of transient paresthesias of the left leg 1 year earlier. In addition, she complained of two episodes of slowly healing “cold sores” in her mouth during the past year. Family history was positive for SLE in her mother, who was said to have died of complications of the disease.

Examination revealed VA of 20/200 OU with bitemporal field loss. MRI of the brain showed multiple white matter lesions and enhancement of the optic chiasm (Fig. 4). ANA titer was positive to a dilution of 1:360 and anti-dsDNA antibody titer was 12.1 U/mL. A diagnosis of SLE was made. She was treated with 5 days of intravenous methylprednisolone followed by oral prednisone taper over several weeks. VA improved to 20/40 OD and 20/30 OS and remained stable 3 months later. The bitemporal defect partially cleared. One year later, the patient developed transverse myelitis, which improved with intravenous corticosteroid treatment. She was placed on monthly cyclophosphamide at that time.
DISCUSSION

We report the clinical course and MRI findings of six patients with visual loss secondary to optic neuropathy or chiasmopathy, the sign that eventually led to the diagnosis of SLE. In two of these patients, visual loss was the first sign of the disease, whereas in the other four, past events had occurred that were consistent with SLE but which were not prominent enough to prompt the diagnosis. The clinical features of these patients are summarized in Table 1.

Although optic neuropathy occurs in only 1% of patients with SLE during the course of their disease, it has been documented as a presenting sign in patients who later meet diagnostic criteria for SLE (1,2,4,5). Involvement of the optic nerve in SLE can occur as acute retrolubar neuritis, papillitis, anterior ischemic optic neuropathy, posterior ischemic optic neuropathy, or slowly progressive visual loss (9). Although none of the patients in our series had previously been diagnosed with SLE, several had notable histories. Patient 3 had 3 months of diffuse joint tenderness 13 years before her optic neuropathy, and patient 2 had a stroke 7 years earlier. Patient 6 had a history of paresthesias and fatigue, as well as a positive family history of SLE. Patient 1 had a previous episode of visual loss in the fellow eye, and patient 5 developed proteinuria. In addition, patients 2 and 6 developed transverse myelitis, and patient 4 experienced psychosis and depression after the diagnosis of SLE was established.

According to the American Rheumatism Association, diagnosis of SLE is established if any four or more of 11 criteria are present serially or simultaneously, during any interval of observation (Table 2) (14). All the patients in our series meet these criteria.

Before optic atrophy has developed, anterior visual pathway disease in SLE may respond dramatically to treatment with corticosteroids. Treatment with intravenous methylprednisolone and either chronic oral steroids or immunosuppressive agents.

MRI characteristics were consistent with those reported by Sklar et al. (8) In their series, six of nine patients with vasculitis-related optic neuropathy and three of six with known SLE demonstrated enlargement and enhancement of segments of the optic nerves and/or chiasm with gadolinium. All but one patient in our series had enhancing lesions of the anterior visual pathways. In the one patient without radiologic evidence of optic pathway abnormalities (case 2), numerous deep and subcortical white matter lesions were present, consistent with previously reported findings in SLE patients with nonfocal symptoms (10).

CNS involvement in SLE may be caused by either small-vessel vaso-occlusive disease and/or hypercoagulability secondary to lupus anticoagulant (3,10). True vasculitis is rare, although histopathologic studies of optic neuropathy in SLE demonstrated focal fibrinoid necrosis of arterioles with perivascular lymphocytic and plasma cell infiltration. Areas of demyelination and gliosis can also be seen, either as primary lesions or a secondary response to focal necrosis (11–13). The MRI appearance of cerebral vaso-occlusive disease is characterized by subcortical white matter changes (10), as seen in several of our patients.

The clinical overlap between neurologic manifestations of SLE and MS is well-known, and many authors believe that there may be a common pathogenesis for both (13,14,15,16). It has been suggested that MS is frequently misdiagnosed as SLE-related CNS vasculopathy and vice versa (17). Further confusing the issue is that fact that as many as 81% of MS patients have a positive ANA titer (18), although usually not to the level found in our patients. This clinical conundrum again surfaces in our patients, who experienced sudden or subacute visual loss with pain, a feature well-known to be common in patients with MS-related optic neuritis and not typically seen in optic neuropathy of vasculopathic origin.

However, there are some factors that may be helpful in distinguishing these two entities. First, although the exact incidence of positive anti-dsDNA titters in MS is unknown, it is surely much less common than in SLE. Even in those MS patients who may have measurable anti-DNA serum antibodies, extremely high levels would not be expected; such a finding would lend much more credence to a diagnosis of SLE. Also, the temporal profile of visual recovery may help to distinguish between these two diseases. In cases of “typical” optic neuritis, the Optic Neuritis Treatment Trial showed a visual recovery to 20/40 or better in 95% of cases, with or without treatment. Such a course was not typical of our patients, and, in fact, many of them required chronic immunomodulation to maintain vision. Even so, VA of 20/40 or better at last follow-up was achieved in only one of three of our patients, and there was a tendency for a slow “step-wise” visual loss. Finally, 50% of our patients were older than 50 years, another factor that is atypical for

<table>
<thead>
<tr>
<th>TABLE 2. American Rheumatism Association 1982 revised criteria for diagnosis of systemic lupus erythematosus</th>
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<tbody>
<tr>
<td>1. Malar rash</td>
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<tr>
<td>2. Discoid rash</td>
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<tr>
<td>3. Photoeasitvity</td>
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<tr>
<td>4. Oral ulcers</td>
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<tr>
<td>5. Arthritis</td>
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<tr>
<td>6. Serositis (pleuritis or pericarditis)</td>
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<tr>
<td>7. Renal disorder (persistent proteinuria or cellular casts)</td>
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<tr>
<td>8. Neurologic disorder (seizures or psychosis)</td>
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<tr>
<td>9. Hematologic disorder (hemolytic anemia or leukopenia &lt;4,000/mmol and lymphopenia &lt;1,500/mmol or thrombocytopenia)</td>
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<td>10. Immunologic disorder (positive LE cell prep of anti-DNA or anti-Sm or false-positive serologic test for syphilis)</td>
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<tr>
<td>11. Antinuclear antibody: abnormal titer at any point in time</td>
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* A minimum of four criteria is needed for diagnosis of SLE.
optic neuritis owing to MS or other demyelinating disease.

Another entity that may present similarly to SLE-associated optic neuropathy is the so-called “autoimmune optic neuropathy” originally described by Dutton et al. (17). They described several patients with visual loss associated with arthralgias, positive rheumatoid factor, or suspicion for other collagen-vascular disease. Similar to our cases, the visual loss in these patients responded dramatically to systemic steroid treatment. However, all their patients were under 50 years of age, their ANA titer was low, and none had detectable anti-DNA antibodies. Autoimmune optic neuropathy may thus be somewhat of a “middle ground” between optic neuritis and SLE-associated optic neuropathy.

Alternatively, the patients described by Dutton et al. may have progressed in the future to develop true SLE or other rheumatologic/collagen-vascular diseases. Patients who may have 10% dysfunction of a joint or a kidney may be asymptomatic and not seek medical attention. However, patients with 10% optic nerve dysfunction typically are acutely aware of visual loss, prompting early presentation to a physician and further investigation. Thus, it is not surprising that patients with optic neuropathy that is ultimately determined to be secondary to SLE (or other vasculitides) may present with visual loss early in their overall disease course, before the formal diagnostic criteria are satisfied.

We believe that all patients with optic neuropathy or chiasmopathy associated with systemic findings not characteristic of demyelinating disease (e.g., arthralgias, leukopenia, skin rash) should be evaluated with gadolinium-enhanced MRI and serologic testing for collagen vascular diseases. In addition, patients with similar presentation but who are atypical for MS (e.g., age >40, poor visual recovery, multiple relapses) should undergo similar testing. Elevated ANA and anti-dsDNA antibody titers strongly suggest a diagnosis of SLE. In such patients, MRI will frequently demonstrate enhancing optic nerve and/or chiasmal lesions. Treatment with high-dose intravenous methylprednisolone should be instituted with close vigilance for relapses during oral steroid taper. Such occurrences may necessitate the use of either chronic steroids or cytotoxic immunosuppressive medications to stabilize or improve vision or to prevent other complications of the vasculitis process. Finally, perhaps consideration should be given to the recognition of optic neuropathy or chiasmopathy, in addition to seizures and psychosis, as a CNS manifestation in the diagnostic criteria for SLE.

REFERENCES

Symptomatic Corneal Topographic Change Induced by Reading in Downgaze

Karl C. Golnik, MD, and Eric Eggenberger, DO

Objective: To elucidate the cause of monocular blur or diplopia after reading in downgaze.

Methods: Corneal topography was obtained before and after a 15- to 30-minute reading effort in downgaze in three symptomatic patients and in nine asymptomatic control subjects.

Results: Changes in corneal topographic color maps, corneal uniformity index, and predicted corneal acuity were found in the symptomatic patients but not in the control subjects before and after reading.

Conclusion: Changes in corneal topography can occur after prolonged reading in downgaze and may produce symptoms of blur or monocular diplopia.

Key Words: Monocular diplopia—Corneal topography.

Monocular blurring or monocular diplopia after prolonged reading has been reported (1-6). Changes in corneal regularity induced by eyelid position or a combination of eyelid position and corneal drying are thought to cause these symptoms. We report three patients who were referred for neuro-ophthalmologic evaluation of blurred vision that occurred only after prolonged reading in downgaze. Transient changes in corneal topography after reading were documented in each patient.

PATIENTS AND METHODS

Three patients were referred for neuro-ophthalmologic evaluation (patients 1 and 2 to The Cincinnati Eye Institute, patient 3 to Michigan State University) with unexplained monocular blurred vision after reading. Their case histories are detailed here. Nine asymptomatic employees with normal ophthalmologic examinations served as controls. The control group ranged in age from 23 to 55 years (mean, 38); four were presbyopic. Patients and controls had complete eye examinations including corneal topography (unmasked). The EyeSys Premier Version 4.2 (EyeSys Technologies, Houston, TX) with the Holladay diagnostic summary was used for each participant except patient 3, who was evaluated with a Computed Anatomy Topographic Modeling System 1 (Tomey). Topography was obtained before and after 30 minutes of reading in downgaze. Presbyopes read through their bifocals and nonpresbyopes were instructed to hold the reading material at a 45-degree downward angle. Measurements of central corneal regularity, corneal uniformity (CU) index, and predicted corneal (PC) acuity (Holladay Diagnostic Summary, EyeSys Technologies) were compared for each subject before and after reading. The CU index is a measure (expressed as a percentage) of the uniformity of distortion of the corneal surface within the 3-mm pupil. Thus, a CU index of 100% indicates that the cornea is perfectly uniform over the central 3 mm. The PC acuity provides a Snellen acuity of the optical quality of the central 3-mm corneal surface. Patient 3 also underwent corneal topography before and after reading in primary position. Institutional (Cincinnati Eye Institute) Review Board Ethics Committee approval was obtained. Formal statistical analysis was not applied because of the small number of symptomatic eyes.

CASE REPORTS

Patient 1

A 47-year-old woman was referred for evaluation of visual distortion and monocular ghosting of images that occurred OD at distance and near after reading through her bifocals for 20 to 30 minutes. These symptoms would
Patient 1
A 28-year-old woman noted a sudden onset of blurred vision OS with near and far objects after reading for 30 to 60 minutes. She was otherwise asymptomatic and healthy except for a childhood seizure disorder. Visual acuity was 20/20 OU at distance and near with -0.50 OU and +1.50 add OU. Examination was normal; no corneal or eyelid abnormalities were noted, and eyelid position was symmetrical in primary position and downgaze. Corneal topography OD showed mild regular astigmatism before reading (Fig. 1). CU index was 100% and predicted corneal acuity was 20/10. Thirty minutes after reading through her bifocals, symptoms occurred and topography had changed (Fig. 1). CU index was 80% and PC acuity was 20/20. Symptoms resolved 60 minutes later, and topography returned to baseline. She obtained full-field reading glasses and read in a chin down position (eyes in primary position). Symptoms have not recurred for 2 years.

Patient 2
A 60-year-old woman noted blurred vision OS in viewing distant and near objects after reading for 20 minutes through her bifocals. She was healthy and taking no medications. Visual acuity was 20/20 OU at distance and near with -2.50+0.50x90 OD and -2.50+0.25x80 OS with +1.75 add OU. Examination was otherwise normal; no corneal or eyelid abnormalities were noted. Corneal topography showed minimal regular astigmatism OS (Fig. 2). CU index was 100% and PC acuity was 20/16. Thirty minutes after reading, topography had changed OS (Fig. 2). CU index had decreased to 80% and PC acuity was 20/25. Symptoms ceased after she obtained full-field reading glasses and read in primary position.

Patient 3
A 71-year-old man complained of blurred vision OS at distance and near after reading for 5 to 10 minutes. He had Cogan's corneal dystrophy OU and had undergone uneventful cataract extraction more than 1 year before presentation. Visual acuity was 20/40 OD and 20/25 OS at distance and near. Other than pseudophakia and Cogan's dystrophy, the examination was normal. Cor-
neal topography OS showed regular astigmatism before reading which increased after reading for 15 minutes through his bifocals in downgaze (Fig. 3). Topography did not change significantly after reading in primary position for 15 minutes (Fig. 4). Symptoms did not recur after switching to single-vision reading glasses and adopting a chin-down position.

RESULTS

Table 1 summarizes the central corneal regularity data for patients and controls. Patients were more likely to develop a worsening CU index and PC acuity than controls after 30 minutes of reading in downgaze. Corneal topographic difference maps best illustrated the changes in topography occurring before and after reading. Topographic difference maps compare two topography measurements in time. A difference map was generated by subtracting the corneal curvature at corresponding corneal points obtained before and after reading. Identical topography before and after reading would result in a

<table>
<thead>
<tr>
<th>TABLE 1. Corneal Topographic Data Before and After Reading</th>
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<td>Patient #</td>
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<td>3*</td>
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<td>Control group</td>
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SD-standard deviation
* Patient 3 was tested on a different topography machine which did not have these data available.
FIG. 4. Computed anatomy topography of patient 3 before (A) and after (B) reading in primary position. The patient did not develop symptoms while reading in primary position. Note the lack of change in topography OS before and after reading.

FIG. 5. Control group EyeSys topographic difference maps comparing before and after reading (right eyes shown). Control group difference maps show a maximum of 1.50-diopter change centrally, whereas the symptomatic subjects had 2.50 diopters.
difference map with a uniform color where each point was zero diopters. A large change over time would result in a multicolored map reflecting a variety of dioptric changes. Qualitatively, the corneal topography difference maps showed more changes after reading in the three patients than they did in the control subjects (Fig. 5).

DISCUSSION

Our three patients presented with transiently blurred vision and/or monocular diplopia with distance and near viewing that only occurred after reading. Each patient read through bifocals and therefore in downgaze. The symptoms resolved 30 to 60 minutes after cessation of reading. Corneal topography changed after the reading effort in downgaze in each patient. No change occurred after reading in primary position in patient 3. (Patients 1 and 2 were not tested after reading in primary position.) Measurements of central corneal regularity (CU index, PC acuity) worsened after reading in downgaze in each patient tested. Symptoms ceased after they switched to a separate pair of full-field reading glasses, which allowed reading in primary position. We concluded that the blurred vision and monocular diplopia were attributable to corneal surface changes induced by prolonged downgaze.

Monocular diplopia usually results from optical irregularities. It is typically described as a ghosting or overlap of images rather than two separate images. The images are usually vertically or obliquely superimposed. Monocular diplopia from optical irregularities should improve with use of the pinhole. The retinoscopic reflex will usually be abnormal.

Fincham (7) found that physiologic monocular diplopia could be demonstrated by 43% of his asymptomatic subjects under the right viewing conditions. He attributed this phenomenon to refractive index differences of the lens substance. Symptomatic monocular diplopia can occur from uncorrected refractive error (8), especially corneal or lenticular astigmatism, lenticular irregularities such as fluid clefts and mild cataract (9), extrapupillary aperture (10), as well as corneal irregularity induced by chalazion (11), eyelid position (12), or excimer laser surgery (13). Nonoptical causes of monocular diplopia are rare and include choroidal neovascularization (14), cystoid macular edema, epiretinal membrane, anomalous retinal correspondence (15), and ocipitoparietal lesions (16).

Monocular diplopia or blurred vision after reading in downgaze was previously described (1–6). Mandell (1) reported a 20-year-old college student who developed monocular blur and double vision after reading for 1 hour. Distortion of keratometer mire image and changes in retinoscopic reflex were noted when symptoms occurred. Knoll (2) reported his own bilateral monocular diplopia that developed after reading. His symptoms could be prevented by supporting his upper eyelids with his thumbs while reading. He did not develop diplopia in the eye he had occluded while reading. Bowman et al. (3) found photokeratographic changes in a patient with monocular diplopia after reading. Kommerell (4) reported 20 patients with monocular diplopia that he believed was attributable to lid pressure. Details of the patient symptoms are only given for one patient who developed these symptoms after reading. The author suggested that eyelid pressure caused a corneal prismatic effect. Ford et al. (6) reported six patients with either monocular diplopia or fuzzy vision after reading and compared them with 20 asymptomatic controls. Based on videokeratoscopy, red reflex, and interpupillary distance measurements, statistically significant differences in corneal flattening, steepening, surface regularity, and surface symmetry were found between symptomatic subjects and controls after reading. These authors attributed the changes to lid position and drying of the cornea. Because we did not use the same topography machine or software as Ford et al. (6), our data are not directly comparable. However, measures of change in central corneal contour and regularity in symptomatic individuals were different from controls in both studies. Ford et al. (6) also measured interpupillary distances in primary position and downgaze. They found a narrower fissure in the subject group than in the control group.

The position of the normal eyelid has been shown to affect corneal topography (17). Changes in topography have been reported before and after surgery for both congenital and acquired ptosis (18–22). Carney et al. (5) studied nine asymptomatic subjects before and after a 15-minute forced eyelid closure. Five subjects developed monocular diplopia, and each had changes in corneal topography. Other forces acting on the eye might affect corneal shape. Refractive error and corneal topographic changes have been reported after strabismus surgery (23–25). Nardi et al. (25) found that 6% of their patients had a more than 1-diopter change in astigmatism 30 days after surgery.

Each of our patients had immediate and persistent resolution of symptoms after obtaining reading glasses that did not require near work in downgaze. Thus, the symptoms must be related to the position of the eye as opposed to the act of accommodation. Presumably forces produced by the eyelid or the extracoronal muscles on the cornea resulted in these transient, symptomatic corneal topographic changes.

REFERENCES


We report a 38-year-old woman with bilateral tonic (Adie’s) pupils who was diagnosed as having Vogt-Koyanagi-Harada syndrome. The tonic pupils persisted after other clinical features of this syndrome had disappeared.

Key Words: Tonic pupils—Adie’s pupils—Vogt-Koyanagi-Harada syndrome.

Vogt-Koyanagi-Harada (VKH) syndrome is an autoimmune disorder characterized by depigmentary inflammation of melanocyte-containing tissues. Findings include bilateral panuveitis with exudative retinal detachment, vitiligo, alopecia, poliosis (patchy whitening of the scalp hair, eyelashes, and eye brows), tinnitus, hearing impairments, and meningismus (1).

Tonic (Adie’s) pupil is characterized by a poor pupillary light reflex, accommodation paresis, strong pupillary response to near stimuli, and slow redilation of the pupil after constriction to near stimuli. Damage to the postganglionic parasympathetic innervation of the intraocular muscles produces this syndrome. Tonic pupils can develop in several conditions such as ocular inflammation, peripheral or autonomic neuropathy, and Adie syndrome (2). Rarely has tonic pupil been described in VKH syndrome (3,4). We report a young woman who developed bilateral tonic pupils associated with VKH syndrome.

CASE REPORT

A 38-year-old woman noticed bilateral visual loss on awakening. She denied any pain on eye movements. She had been well without significant medical history. Initial ophthalmologic evaluation revealed visual acuity of count fingers at 2 m in the right eye (OD) and 20/200 in the left eye (OS). Both pupils measured 7 mm, and there was no light reaction. Slit-lamp examination showed inflammatory cells in the anterior chamber and vitreous body. Posterior synechia was not present. Both optic disks were hyperemic and swollen. The retinal vessels were tortuous. Macular edema was noted in both eyes, but exudative retinal detachments were not observed. Visual evoked potentials (VEP) revealed delayed response in both eyes. She was diagnosed as having bilateral optic neuritis and uveitis and treated with a topical steroid and oral prednisolone for 1 month. Approximately 1 week after symptom onset, she developed severe headache with nausea, vomiting, and myalgia. Over the next 2 months, her visual acuity improved, and examination showed no inflammatory cells in the anterior chamber and vitreous body. However, her unreactive and dilated pupils remained unchanged.

At this stage, she was referred to a neuro-ophthalmology clinic for evaluation of persistent bilateral pupillary mydriasis of unknown cause. She complained of persistent blurred vision and photophobia while reading. She reported severe hair loss during the acute phase of her illness. She denied tinnitus or hearing loss.

Neuro-ophthalmologic examination revealed vitiligo and poliosis in the hair and upper eyelashes that had evidently developed well after the acute phase of her illness (Fig. 1A). She had visual acuity of 20/20 in each eye (OU) with normal visual fields and full ocular motility. Near visual acuity was 20/25 OU. Both pupils were 7 mm and unreactive to light and near targets. Fundus examination showed normal discs and maculae. The general neurologic examination was normal including deep tendon reflexes. Thirty minutes after instillation of one
FIG. 1. A: Patchy whitening (poliosis) of upper eyelashes (arrow). B: Thirty minutes after instillation of one drop of 0.125% pilocarpine, the left pupil demonstrates denervation supersensitivity by constricting from 7 to 3 mm drop of 0.125% pilocarpine OS, the pupil constricted to 3 mm (Fig. 1B). Follow-up VEP was normal. She also had normal brain magnetic resonance imaging, C-reactive protein, and antinuclear antibody. Based on the combination of tonic pupils, vitiligo, poliosis, and the history of uveitis, retinal edema, and optic neuritis, VKH syndrome was diagnosed.

Three months later, or 6 months after symptom onset, both pupils measured 6 mm and began to react to light and near targets, although she still experienced blurred vision in the daylight. The pupils constricted more strongly with near stimuli than with light and showed slow redilation after viewing near targets. The poliosis had almost resolved, leaving the tonic pupils as the only residual sign of VKH syndrome.

DISCUSSION

Tonic pupils can be associated with a variety of inflammatory and infectious disorders that damage the ciliary ganglion alone or as part of a systemic process. VKH syndrome is a systemic disease affecting the uvea, retina, meninges, and skin. Associated neurologic findings are cranial nerve palsies, horizontal nystagmus, diminished labyrinthine function, sensorineural hearing loss, tinnitus, and increased vestibulo-ocular reflex (5).

Tonic pupils have rarely been reported in this syndrome (3,4). The pupillary tonicity in VKH syndrome may be owing to degeneration at the ciliary ganglion or involvement of short ciliary nerves owing to the diffuse ocular inflammation. This is presumably followed by aberrant reinnervation.

VKH syndrome takes a course that can be divided into three stages: the meningeal (prodromal), the ophthalmic, and the convalescent stage (6). The characteristic skin and hair manifestations such as vitiligo, poliosis, and alopecia usually develop in the convalescent stage, approximately 2 to several months after symptom onset (1).

In our patient, the only residual ophthalmologic finding was bilateral tonic pupils when the diagnosis of VKH syndrome was made. Tonic pupils in VKH syndrome may be transient, lasting several months, or can persist more than a year (3,4). Our patient had visual blurring and photophobia from tonic pupils even after resolution of the poliosis. In patients with tonic pupils, preceding or accompanying symptoms and signs of VKH syndrome should be sought.

REFERENCES

Relative Pupil-Sparing Oculomotor Nerve Palsy as the Presenting Sign of Posterior Fossa Meningioma

Jacqueline M. S. Winterkorn, MD, PhD. and Michiko Bruno, MD

We report a case of relative pupil-sparing oculomotor paresis initially attributed to ischemia because weakness of other cranial nerves was minimal and dismissed as insignificant. Neuroimaging eventually revealed a posterior fossa meningioma. The neurologic symptoms and signs disappeared immediately after resection of the tumor. The third nerve palsy was attributed to deformation of the brainstem. This case reinforces the importance of neuroimaging even in patients who have apparently isolated oculomotor palsy with features not classic for an ischemic etiology.

Key Words: Oculomotor nerve—Third nerve palsy—Meningioma.

CASE REPORT

A 68-year-old woman without diabetes, hypertension, or other medical problems became aware of diplopia. Within a day or two, she noticed her right eyelid drooping, and within 3 days her eyelid was closed. She consulted an ophthalmologist and a neurologist who diagnosed an isolated right pupil-sparing third nerve palsy. Her complete blood count and blood chemistries were normal and the erythrocyte sedimentation rate was 30. A vasculopathic basis was presumed; neuroimaging was considered unnecessary and she was started on a daily aspirin.

Reexamination 3 weeks later disclosed a best-corrected visual acuity of 20/30 OD and 20/15-2 OS. Visual fields on a Humphrey 24-2 threshold test showed superior constriction OD. The pupils were 3 mm OD and 3.25 mm OS, both reactive, but the right pupil was a bit sluggish. There was no afferent pupillary defect. The OD had reduced adduction, supraduction, and infraduction; abduction was intact. The OS had intact ductions. A left hyperdeviation was present in upgaze, a right hyperdeviation in downgaze, and an exodeviation in left gaze. The right upper lid had 5 mm of proptosis. The fundus was normal.

Neurologic examination revealed trace facial asymmetry, with incomplete burial of the lashes OS on forced eyelid closure (Fig. 1). Hearing to whispered voice was subjectively decreased in the right ear. The palate elevated slightly less on the right, and the tongue deviated slightly to the right (Fig. 2). A trace left pronator drift was demonstrated. The patient also had a tendency to turn toward the right when marching in place with eyes closed. These findings had been dismissed at the initial neurologic examination as variations of normal. Magnetic resonance imaging of the brain (Fig. 3) demonstrated a large left posterior fossa meningioma with herniation of the cerebellar tonsils through the foramen magnum. The meningioma was resected. Two days postoperatively, all neurologic manifestations had resolved.

DISCUSSION

Oculomotor nerve palsy can be caused by ischemia, trauma, or compressive lesions such as aneurysms, cavernous sinus meningiomas, other primary tumors, or metastases (1-4). The finding of greatest diagnostic significance is often considered to be the involvement or sparing of the pupil (5). Oculomotor nerve pareses that spare the pupil are usually attributed to microvascular ischemia, commonly associated with diabetes or hypertension (6). Such pupil-sparing third nerve pareses usually resolve within three months and require no intervention other than palliating the diplopia and managing the vasculopathic risk factors. Conversely, pupil paresis signals compression by tumors and aneurysms, requiring angiography and sometimes surgical intervention. Although rare cases have been reported in which pupil-sparing oculomotor nerve palsy was owing to aneurysm, Rucker’s rule is based on the statistic that 95 to 97% of
aneurysms causing third nerve palsy produce pupillo­paresis (1,2,7).

Our patient was initially diagnosed with ischemic pupil­sparing oculomotor nerve palsy because subtle signs of other cranial neuropathies were dismissed as variants of normal. However, other clues should have prompted doubt about the diagnosis of microvascular ischemia. Although the patient was 60 years old, she had no arteriosclerotic risk factors. Her extraocular muscle palsy, especially of the inferior rectus, was not complete. The pupillary reaction to direct light in the ipsilateral eye was sluggish, suggesting relative rather than absolute pupil sparing. Trobe (8) pointed out that the rule associating pupil-sparing with an ischemic cause should be applied cautiously, with attention to four exceptions to the rule: 1) age between 20 and 50 or lack of obvious arteriosclerotic risk factors, 2) an incomplete extraocular muscle palsy, 3) relative pupil sparing, and 4) a nonisolated third nerve palsy.

In our case, the relative pupil-sparing oculomotor nerve paresis was caused by a distant contralateral posterior fossa meningioma, so that direct oculomotor compression was unlikely. Yet we believe the palsy was caused by the tumor insinu​mah as the palsy cleared promptly after tumor removal. The most likely cause of the palsy was stretching of the oculomotor nerve within the subarachnoid space as it emerged from the brainstem in the interpeduncular fossa. Meningiomas can cause false localizing signs by displacing and stretching (9). This patient's tumor was pushing the cerebellum caudally and ventrally, causing the pons and medulla to deviate rightward and downward toward the foramen magnum. These actions placed the cranial nerves on stretch. A case of pupil-sparing oculomotor nerve palsy from ipsilateral acute subdural hematoma has been reported, the mechanism presumed to be mass effect on the subarachnoid portion of the oculomotor nerve (10).

Several hypotheses can be considered to explain the pupil sparing, which was an unusual feature of this case because pupil involvement is thought to be the earliest manifestation of third nerve palsy secondary to stretch or pressure (9). In the case of pupil-sparing oculomotor nerve palsy from acute subdural hematoma mentioned previously, Kavieff et al. (10) suggested anatomic positioning within the third nerve or sheltering of pupillomotor fibers from the tentorial gap. In our case, if the forces from the tumor were exerted laterally and inferiorly as the nerve exited the brainstem, the pupillary fibers that emerge more ventrally from the Edinger-Westphal nucleus and travel medially and superiorily might be preserved (11).

The combination of pupil sparing with incomplete inferior rectus palsy is similar to the case reported by Fleet...
et al. (12) and adds evidence for the proximity of the inferior rectus fibers to the pupillary fibers in this proximal portion of the oculomotor nerve after its emergence from the brainstem. Alternatively, as hypothesized by Nadeau and Trobe (5), the small-caliber unmyelinated parasympathetic pupillomotor fibers may be more resistant to injury by slow stretch. This possibility is supported by the finding that in peripheral nerves, the mechanism of nerve injury by stretch is focal demyelination (13). Finally, the oculomotor nerve could have been stretched more distally in the subarachnoid space. In that case, pressure exerted laterally rather medially, as is usual for carotid aneurysms and cavernous lesions, could have spared the dorsomedially situated pupillary fibers.

Any deviation from the typical ischemic oculomotor nerve palsy, including duration, age, incomplete extracocular palsy, relative pupil-sparing, and any other associated neurologic signs, requires further investigation. Associated signs may be very subtle; repeated careful neurologic examination is necessary.

REFERENCES
Ocular Myasthenia Mimicking a One-and-a-Half Syndrome

Fabio Bandini, MD, David Faga, MD, and Stefano Simonetti, MD

A 52-year-old patient developed an eye movement disorder first resembling a left internuclear ophthalmoplegia and subsequently a “one-and-a-half syndrome” as the presenting symptoms of ocular myasthenia gravis. No accompanying myasthenic features were present except for the fluctuation in the amplitude of dissociated nystagmus. This patient shows that an oculomotor disorder considered a typical pontine lesion may instead be caused by myasthenia gravis, even in the absence of other clinical and electrophysiologic features of neuromuscular deficit.

Key Words: Pseudo one-and-a-half syndrome—Pseudo internuclear ophthalmoplegia—Myasthenia gravis.

Unilateral lesions of the pontine tegmentum affecting the abducens nucleus or paramedian reticular formation and the ipsilateral medial longitudinal fasciculus cause internuclear ophthalmoplegia (INO) and ipsilateral horizontal gaze palsy, a clinical feature known as “one-and-a-half syndrome.” The most common causes of INO and one-and-a-half syndrome are stroke in the elderly and multiple sclerosis in the young, but brainstem tumors, subdural hematoma, head trauma, and Arnold-Chiari malformation have been reported to produce them as well (1). The term pseudo INO was introduced by Glaser (2) to designate an INO-like disorder in a patient with myasthenia gravis (MG). Since then, a few cases of unilateral pseudo INO in MG have been reported (3–6).

We describe a case of an eye movement disorder mimicking at first INO and then a one-and-a-half syndrome in a 52-year-old man that resulted from ocular myasthenia.

CASE REPORT

A 52-year-old man with a history of hypertension was admitted to our department because of the occurrence of diplopia and blurring of vision on right horizontal gaze. His medications included fosinopril and hydrochlorothiazide. His neurologic history was unrevealing. Upon admission, he had impaired adduction OS and a horizontal right-beating nystagmus OD on rightward gaze (left INO). Although he did not complain of fatigability or fluctuation of the symptoms, the amplitude of the dissociated nystagmus varied with each examination. Oculocephalic stimulation could not improve the defective eye movements. Convergence was relatively spared. Skew-deviation and ptosis were absent. Leftward gaze and vertical eye movements were normal. The pupils were equal and normally reactive to light and convergence accommodation. The optic disks were normal. Monocular distance acuity was 20/20. The remainder of the neurologic examination was negative.

Two days later, the patient started complaining of difficulty gazing to the left as well. In addition to the above-described findings, leftward gaze palsy was present. Dissociated nystagmus in abduction OD was still present and fluctuating in amplitude. This new oculomotor pattern was consistent with a one-and-a-half syndrome. Oculocephalic stimulation was again unable to improve the eye movement disturbance. On suspicion of an expanding lesion of the left pontine tegmentum, a brain magnetic resonance imaging with gadolinium was performed but did not show any lesion in the cerebellum or brainstem or abnormalities of the eye muscles (not shown because negative but available). Cerebrospinal fluid examination was also negative.

Intravenous administration of edrophonium chloride (Tensilon), 1.0 mg, completely resolved the gaze palsy. A computed tomography scan of the chest with contrast showed no thymus gland. Antibodies to acetylcholine receptor and to skeletal muscle, antinuclear antibody, serum VDRL, and thyroid functions were negative. Repetitive stimulation (3 Hz) of the ulnar, musculocutaneous, and facial nerves before and after exercise and

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single-fiber electromyography (EMG) of the orbicularis oculi were unrevealing. Single-fiber EMG of the extraocular muscles was not performed. Negativity of laboratory and imaging examinations allowed us to exclude other possible diagnoses, and, based on the positive response to Tensilon, a diagnosis of ocular myasthenia was made. The patient was given pyridostigmine, starting with 60 mg daily, increased to 180 mg daily. At those doses, there was complete control of the oculomotor symptoms. When last examined, 1 year after the onset of the disease, the patient had a normal neuro-ophthalmologic examination.

**DISCUSSION**

Our patient manifested a neuromuscular eye movement disorder that started with a left pseudo INO and later evolved into a pseudo one-and-a-half syndrome, with no accompanying myasthenic features except for the fluctuation in the amplitude of dissociated nystagmus. The only other case of a pseudo one-and-a-half syndrome owing to myasthenia is the one reported by Davis and Lavin (7). In the latter, however, late ptosis occurred that was helpful in the differential diagnosis.

This case suggests that, although uncommon, MG should be considered in the differential diagnosis of oculomotor disorders usually associated with brainstem lesions, including one-and-a-half syndrome. Importantly, this can be the case even in absence of any other manifestation of ocular myasthenia gravis, i.e., fatigue, ptosis, impaired convergence, and a decremental electromyographic response to repetitive nerve stimulation.

**REFERENCES**

Isolated Unilateral Post-traumatic Internuclear Ophthalmoplegia

Jane W. Chan, MD

A patient developed an isolated unilateral internuclear ophthalmoplegia (INO) after head trauma. An uncommon complication of closed head trauma, INO usually occurs bilaterally and is often associated with other neurologic deficits. The mechanism may be shear injury caused by angular acceleration leading to downward displacement of the posterior brainstem downward, stretching of the nerve fibers of the medial longitudinal fasciculus, or compression and tearing of its arterial supply.

Key Words: Internuclear ophthalmoplegia—Head trauma.

Internuclear ophthalmoplegia (INO) is characterized by paresis of adduction on lateral gaze with horizontal jerk nystagmus in the contralateral abducting eye. Vertical nystagmus during upward gaze may be present (1). Approximately 3 to 7% of patients with head injuries have ocular motor palsies, most commonly of the third, fourth, and sixth cranial nerves. Nystagmus, skew deviation, supranuclear palsy, conjugate deviation of the eyes, and impaired convergence are less frequently observed (1). INO is an uncommon complication of closed head trauma, with only 13 documented cases, four of which were unilateral. Of the four unilateral cases, two were associated with other neurologic findings (1,2). This case report describes a patient with isolated unilateral INO from a medial longitudinal fasciculus (MLF) infarct immediately after blunt head trauma.

CASE REPORT

A 32-year-old man was assaulted, sustaining injury to the right side of his head that caused loss of consciousness for several hours. He had a right mandibular fracture and right periorbital edema. His corrected visual acuity was 20/20 in both eyes. Pupillary responses and Humphrey automated visual field testing were normal. Ocular motility examination demonstrated orthophoria in primary position. His right eye was unable to adduct and his left eye had abduction nystagmus during leftward gaze. The nystagmus had a vertical and rotary component in upgaze. Convergence was not spared. Forced duction testing revealed no restriction. He had no other neurologic abnormalities.

Orbital computed tomography (CT) revealed no orbital fractures. Magnetic resonance imaging (MRI) of the brain with contrast revealed a right hyperintense MLF lesion on axial T2-weighted images (Fig. 1). Gradient echo MRI showed no evidence of primary brainstem hemorrhages or secondary Duret hemorrhages. Diffusion-weighted imaging suggested that the MLF lesion was an acute infarct.

Cerebrospinal fluid (CSF) cell count, protein, and glucose were all within normal limits. CSF venereal disease research laboratories test, Gram stain, acid-fast bacilli stain, and bacterial antigens for Haemophilus influenzae, Neisseria meningitidis, and Streptococcus pneumoniae were all negative; routine bacterial, viral, and fungal cultures were also negative. A CSF multiple sclerosis panel, including immunoglobulin G (IgG) index, CSF IgG synthesis rate, oligoclonal immunoglobulin bands, and myelin basic protein, was within normal limits.

Three months later, he had a mild adduction deficit OD and residual horizontal diplopia in left gaze. Six months later, he had gained almost full recovery.

DISCUSSION

Bilateral INO resulting from head trauma is more commonly reported than is unilateral INO. Unilateral INO without any associated neurologic deficits, as in the patient described here, is a very rare complication of blunt head trauma. Our patient presented with slowed adducting saccades OD and abducting nystagmus OS. The vertical and rotary component of this abduction nystagmus on upgaze and the presence of a right MLF signal abnormality on MRI support a central rather than a peripheral cause such as a partial third nerve palsy. The
absence of orbital fractures and restriction on forced duction testing exclude an extraocular muscle entrapment.

The pathogenesis of isolated damage to the MLF in head trauma is unclear, but several mechanisms have been suggested to explain this phenomenon. Shearing forces from angular acceleration or deceleration of the head on impact can stretch the nerve fibers of the MLF (3). The shearing forces exert maximal effect where the difference in density between CSF and adjacent neural tissue is greatest (3). Because the MLF is situated near the aqueduct and the floor of the fourth ventricle, it is vulnerable to these shearing forces. The posterior portion of the brainstem is also downwardly displaced more than the anterior portion during rapid acceleration/deceleration because the anterior portion is tethered by small penetrating arteries of the basilar artery, as reported in experimental angiographic studies (4). The shearing forces can therefore create a temporary downward displacement of the posterior brainstem, causing shear injury to the MLF. Furthermore, the shear forces within the brainstem could damage the perforating branches of the basilar artery, resulting in decreased blood flow or focal brainstem hemorrhage.

MRI correlation of structural lesions with the described possible mechanisms has been shown in only a few previously documented cases of posttraumatic INO. In two cases, Strauss et al. (5) showed that a unilateral INO after head trauma could be a result of a pontomesencephalic hemorrhage as seen on MRI and CT. In this report, we demonstrate that an infarct of the right MLF was probably responsible for the unilateral INO immediately after head trauma. This lesion was seen as a bright signal on the T2-weighted image (Fig. 1) and as a T1-weighted dark signal with gadolinium enhancement. Diffusion-weighted imaging also helped to confirm this lesion to be an acute infarct. Other reported cases of posttraumatic INO in the literature either had no verification by neuroimaging or had no visible lesion on CT or MRI, suggesting that direct stretch injury to the MLF could cause a lesion too small to be detected by MRI (1,2,6,7).

More extensive brainstem dysfunction accompanying a posttraumatic INO can include upper extremity ataxia, gait ataxia, and cranial nerve palsies, such as a third nerve palsy with a dilated pupil (8). The damage to the brainstem may result from a remote lesion such as a subdural hematoma, which may lead to transtentorial herniation, pyramidal tract signs, and various cranial nerve palsies (9). This patient had no neurologic abnormalities except an INO.

Dosslak et al. (10) showed that a unilateral posttraumatic INO could fully resolve in 18 weeks. This patient described here had residual horizontal diplopia and a mild adduction deficit after 3 months with almost full recovery after 6 months. As demonstrated by quantitative oculography, central nervous system plasticity, manifested as adaptive firing patterns in response to the MLF lesion, helps in this recovery by increasing and then later normalizing the saccadic pulse duration. As the firing frequency of the pulse and step increases and the conduction of MLF axons improves, greater saccadic gain and velocity are also attained for normal recovery (10).

When an acute head trauma patient presents with an adduction deficit, an INO should be considered as a cause.

REFERENCES

Innervation of the Sternocleidomastoid and Trapezius Muscles by the Accessory Nucleus

John C. DeToledo, MD, and Noble J. David, MD

Images moving over the retina at velocities as low as a few degrees per second, in movements as head turning, can degrade visual acuity. Visual acuity requires that even minute motion of the head be compensated for, primarily via optokinetic and vestibular reflexes. Whereas we have a good understanding of some the neuronal networks involved in these reflexes, other components of this network, such as the innervation of the paired muscles that turn and tilt the head, are not as well understood. The involvement of the sternomastoid, cleidomastoid, or trapezius muscles with lesions of the cervicomedullary junction is often not in conformity with the prevailing neuroanatomic descriptions of their innervation by the accessory nuclei. We discuss evidence that: 1) the XI nucleus has a rostral and a caudal portion; 2) analogous to the VII nerve, the rostral portion receives projections from both cerebral hemispheres, whereas the caudal portion is innervated preferentially by the contralateral hemisphere; 3) the caudal XI nucleus innervates the ipsilateral cleidomastoid and trapezius with a predominantly crossed corticonuclear innervation; and 4) The rostral XI nucleus innervates both sternomastoids. Each rostral portion receives projections from both cerebral hemispheres. These anatomic features explain the seemingly discrepant findings in patients with cervicomedullary lesions.

Key Words: Sternocleidomastoid—Trapezius—Spinal accessory nerve—Anatomy—Head turning—Head and eye movements.

The human sternocleidomastoid is classically described as a single muscle with two attachments of origin—one sternal and one clavicular. From the embryology and comparative anatomy standpoint, however, there is little doubt that the sternocleidomastoid is formed by two separate muscles, the sternomastoid and the cleidomastoid (1–3). In some species, including primates, the sternomastoid and the cleidomastoid blend in a common muscle body near their skull insertion. In other species, however, the two muscles remain separate (i.e., the cleidocephalicus and sternocephalicus muscles in long-neck ungulates, camel, giraffe, and llama), demonstrating their distinct ontogeny (1,2). The XI nucleus also shows variability between species, and its presence appears to be ultimately determined by posture and mode of ambulation (4). In the absence of a forelimb, such as in apodal species (i.e., serpents), the nucleus is absent.

CORTICAL REPRESENTATION OF THE STERNOMASTOID, CLEIDOMASTOID, AND TRAPEZIUS

Hemispheric strokes are frequently associated with weakness of the contralateral trapezius, weakness of head tilting toward the side of hemiplegia, and weakness of the contralateral trapezius. Frontal lobe seizures may initiate as an isolated head turning, via the sternomastoid, or as an isolated head tilting, via the cleidomastoid (5), suggesting that the sternomastoid and cleidomastoid have distinct cortical representations. Seizures that begin with head tilting usually present with concomitant elevation of the ipsilateral shoulder. The cleidomastoid and trapezius muscles appear to have only minor representation in the motor strip (6). Stimulation to the supplementary motor cortex in the interhemispheric fissure more often recruits the cleidomastoid and trapezius, resulting in contralateral head tilting and elevation of the shoulder rather than classic versive head movements (5,6). Contralateral head tilting or shoulder elevation with stimulation of the frontal convexity had not been observed during intraoperative stimulation or with the use of chronic subdural grids (6).

CORTICONUCLEAR PATHWAYS TO THE CLEIDOMASTOID AND TRAPEZIUS

The corticonuclear fibers to the cleidomastoid and trapezius seem to follow the pyramidal pathway through the
innervation of the sternocleidomastoid and trapezius muscles

The organization of the cervical muscles and their innervation by the XI nucleus is determined by posture and mode of ambulation (Fig. 1) (4). The presence of the XI nucleus in a given species seems to depend on whether the presence of a forelimb for the nucleus is absent in the apodial species (i.e., serpents) (9). The implications of the anatomic configuration of the human neck and shoulder is readily apparent during movements such as sideward head turning, which in quadrupeds, corresponds to lateral head tilting in humans; flexion/extension movements of the head in the upright position synergistically use muscles that are reciprocally innervated as agonist-antagonists for horizontal rotation.

The sternomastoid, cleidomastoid, and trapezius muscles are innervated by the accessory nuclei. Similar to the facial nucleus, the accessory nucleus is formed by sparse aggregates of neurons, which can be histologically identified as a rostral portion and a caudal portion (3). The XI nucleus gives origin to the XI nerve by fusing the exiting root funiculi into a common stem. Although it has not been conclusively demonstrated in humans, the caudal portion of the XI nucleus innervates the cleidomastoid and trapezius muscles in most species, including lower primates (1). Regarding the sternomastoid, the most convincing indication that its innervation originates in the rostral XI nucleus derives from observations in comparable anatomy. Willemse (2) demonstrated that the muscle analogous to the sternomastoid in ungulates is innervated by the rostrally situated ramus ventralis of the XI nerve, which also innervates the palatopharyngeal muscle (Hallet M, Management of myoclonus, Paper presented at the Proceedings for Parkinson’s Disease and Other Movement Disorders, Vail, 1989). The concomitant involvement of the palatopharyngeal and sternomastoid muscles (Hallet M, Management of myoclonus, Paper presented at the Proceedings for Parkinson’s Disease and Other Movement Disorders, Vail, 1989) lends further support to the notion that the innervation to the sternomastoid originates in the rostral XI nucleus. Sparing of the sternomastoid in cases where there is loss of cleidomastoid and trapezius because of cervical lesions (9) lends further support to the notion that the innervation to the sternomastoid originates more rostrally within the XI nucleus. The analogy between the facial nucleus and the XI nucleus, therefore, goes beyond the rostral and caudal division. The rostral part of the XI nucleus innervates the sternomastoid muscles (which receive input from both cerebral hemispheres), whereas the caudal portion of the XI nucleus innervates the cleidomastoid and trapezius muscles (which are innervated primarily by the contralateral hemisphere).

TOPOGRAPHY OF LOWER MOTOR NEURONS WITHIN THE ACCESSORY NUCLEUS

The existing neuroanatomic and neurophysiologic observations provide compelling evidence that 1) the sternomastoid and cleidomastoid are distinct muscles with distinct actions and distinct cortical representations; 2) the XI cranial nerve nucleus has a rostral portion and a caudal portion, and similar to the VII cranial nerve, the rostral portion receives projections from both cerebral hemispheres, whereas the caudal portion is preferentially innervated by the contralateral hemisphere; 3) the caudal portion of the XI nucleus supplies the ipsilateral cleidomastoid and trapezius muscles and receives a predominantly crossed innervation; 4) the tracts to the caudal XI nucleus originate in an area of the cortex that is distinct, located more anterior and mesial to that which innervates the sternomastoid; and 5) the rostral portion of each XI nucleus innervates both sternomastoids. Each rostral portion receives projections from both cerebral hemispheres mainly from the prorolcand cortices located anterior to the thumb and face areas. This cortical area is responsible for the volitional rotation of the head toward both sides but with greater strength contralaterally, and when activating the sternomastoids simultaneously with equal strength, produces anterior flexion of the neck.

CONCLUSION

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Bilateral Cysticercosis of the Optic Nerve

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Bilateral cysticercosis of the optic nerves affected a man who presented with features suggestive of optic neuritis. Ultrasonography revealed bilateral sonolucent cystic lesions with central echo-dense, highly reflective structures behind the optic nerve heads. A subretinal cyst was present in one eye. Magnetic resonance imaging of the brain and orbit revealed multiple cysticerci in the brain, orbit, and eye. The subretinal cyst was removed by pars plana vitrectomy, and the other cysts resolved on treatment with albendazole.

Key Words: Optic nerve—Cysticercosis—Optic neuritis—Albendazole.

Cysticercosis is an infestation by the larval form of the pork tapeworm Taenia solium. It can affect any part of the body, including the heart, muscles, liver, brain, orbit, and eyes. In the eye, cysts may lodge in the vitreous, conjunctiva, or extraocular muscles (1) but rarely in the optic nerves (2). Unilateral, but not bilateral, cysticercosis of the optic nerve has been reported (2–4). We describe a case of bilateral optic nerve cysticercosis, together with subretinal and multiple brain cysts.

CASE REPORT

A 29-year-old man presented reported sudden loss of vision and floaters in both eyes. Visual acuity was light perception bilaterally. The anterior segments were normal. Eye movements were full but painful. Fundus examination revealed bilateral blurring of disk margins along with swelling of the optic disks and a subretinal cyst in the superonasal equatorial region OD. The cyst showed movement when illuminated by flashes of light from the indirect ophthalmoscope. The neurologic examination was normal apart from the ophthalmic findings.

Ultrasonography revealed bilateral disk swelling (Fig. 1a,b) along with sonolucent well-defined cystic lesions with central echo-dense, highly reflective structures behind the optic nerve heads bilaterally (Fig. 1c,d) as well as subretinally on the right side (Fig. 1e,f). Magnetic resonance imaging of the head and orbit revealed bilateral multiple cysticerci of the optic nerves, brain, and orbit (Fig. 2). Based on these findings, the diagnosis of ocular and neural cysticercosis was made. The patient was treated with 60-mg oral prednisolone once daily along with 200-mg oral albendazole three times daily. The subretinal cysticercosis was removed by pars plana vitrectomy. After four weeks of treatment, the disk edema and blurring of the optic disk margins disappeared, and imaging evidence of neural cysticercosis and optic nerve cysticercosis resolved with visual acuities of 6/60 in both eyes.

DISCUSSION

This report documents a case of bilateral optic nerve cysticercosis. Even unilateral cysticercosis of the optic nerve is rare; only three case reports have been published (2–4). To the best of our knowledge, this is the first case report of bilateral optic nerve cysticercosis. Earlier cases of unilateral optic nerve cysticercosis were initially believed to be optic nerve tumors. Our patient presented with features more suggestive of optic neuritis. Ultrasonography, a cystic lesion typical of cysticercosis was detected, which was further supported by magnetic resonance imaging. Because our patient had bilateral loss of vision, he was treated with oral albendazole along with prednisolone. Albendazole is the currently preferred therapy for neurocysticercosis (5,6) and has been reported to produce regression of neurocysticercosis and myocysticercosis (5–8).

However, there are reports of complications such as nausea, vomiting, and headache (9) as well as optic neuritis owing to lysis of cyst in the vicinity of optic nerve (10). Therefore, short courses of albendazole (3–8 days)
were recommended by Sotelo et al. (9). Our patient responded well to medical therapy without any toxic effects. Regarding the subretinal cyst, removal by pars plana vitrectomy remains the preferred method (11).

In cases that suggest bilateral optic neuritis, cysticercosis should be kept in the differential diagnosis, especially in endemic areas. Ultrasonography, magnetic resonance imaging, and other hematologic studies are the investigations of choice. Once the diagnosis is confirmed, a course of albendazole and corticosteroid is recommended.

REFERENCES

Photo Essay

Downbeat Nystagmus Associated with Caudal Brainstem Compression by the Vertebral Artery

Andrew G. Lee, MD

An 87-year-old white man presented with a one-year history of oscillopsia owing to primary position down-beat nystagmus. Visual acuity was 20/20 OU. Pupils, slit-lamp biomicroscopy, visual-field testing, intraocular pressure, and ophthalmoscopy were normal OU. Motility examination showed full versions, and the patient was orthotropic in the diagnostic positions of gaze. In primary position, he had low amplitude, low-frequency downbeating nystagmus. The amplitude and frequency of the downbeat nystagmus were maximal in downgaze and lateral gaze and minimal in upgaze. He was not taking lithium or any other medications. Magnetic resonance imaging of the head revealed compression of the

FIG. 1. A: Axial T2-weighted magnetic resonance imaging (MRI) shows compression of the medulla (arrow) by the vertebral artery. B: Sagittal T1-weighted MRI shows distortion of the caudal brainstem by the vertebral artery flow void (arrow).
caudal brainstem by the vertebral artery (Fig. 1). He declined any intervention.

Downbeat nystagmus is often owing to a lesion at the cervicomedullary junction (e.g., Chiari malformation, platybasia, basilar invagination, Paget's disease). Other causes for downbeat nystagmus include medicines (e.g., lithium), deficiencies of magnesium or $B_12$, alcohol-related disease (e.g., Wernicke's, cerebellar degeneration), demyelination, infarction, hereditary and familial cerebellar degeneration, and neoplasm. Downbeat nystagmus attributable to dolichoectatic vertebral arteries and brainstem compression is rare. Himi et al. (1) reported a case that improved after neurovascular decompression. Krespi et al. (2) reported a case with distortion of the anterolateral medulla by vertebrobasilar dolichoectasia. Jacobson and Corbett (3) reviewed 41 cases of downbeat nystagmus and found two cases of dolichoectasia of the vertebral artery. Clinicians should be aware that caudal brainstem compression owing to vertebral artery dolichoectasia may cause downbeat nystagmus.

REFERENCES

An Interview with Ronald M. Burde, MD, Outgoing Editor-in-Chief (1994–2001), *Journal of Neuro-Ophthalmology*

Jonathan D. Trobe, MD

Ronald M. Burde, MD, retired this year as the Editor-in-Chief of the *Journal of Neuro-Ophthalmology*. He had inherited the journal in 1994 from its founding editor, J. Lawton Smith, MD.

Born in the Bronx, NY, and brought up in Connecticut, he attended the Massachusetts Institute of Technology (BS, 1960) and Jefferson Medical College (MD, 1964). He completed his ophthalmology residency at Washington University in 1968, and, after a 2-year neuro-ophthalmology and glaucoma fellowship there, took over the neuro-ophthalmology service with the support of Andrew J. Gay, MD. After building the service to international renown, he left in 1988 for New York City to become chair of the Department of Ophthalmology, Albert Einstein College of Medicine. This fall he retired from that position, having secured major endowment for the program and compiled an enviable roster of academic honors. The following excerpts are drawn from an interview conducted at his home on May 16, 2001.

**JDT:** As you look back, what do you consider your finest achievement?

**RMB:** The well-trained residents and fellows who have worked with me and gone out into the world. I’ve tried to teach them a mixture of science and humanism. You have to have science, but if you don’t feel something for the patient and make the patient feel better, you’re just a good doctor, not a great physician.

**JDT:** How have medicine and ophthalmology changed since you started?

**RMB:** Less teaching, more unnecessary surgery, over-testing and increasing charges—40 cataracts per day. That is commerce, not medicine.

**JDT:** Do you see that changing?

**RMB:** Yes, we’re passing through a dismal era. The time will come when the money will run out and we’ll go back to doing what we were trained to do—prevent and treat disease, not chase dollars.

**JDT:** How is that change going to happen?

**RMB:** A single key payor system or a socialized system will evolve. Involved professional societies—ophthalmology, optometry, opticianry—will work together to create a delivery system the public can afford.

**JDT:** Don’t prepaid health plans already do that?

**RMB:** Yes, but health planners including academic physicians will have to decide how much and what type of eye care is necessary and enforce the rules.

**JDT:** Will doctors accept that kind of dictatorship?

**RMB:** Yes, when their income falls enough. It is and it will even more.

**JDT:** What about academic medical centers? Are they in danger?

![MIT Graduation, 1960](image-url)
RMB: The danger is that the education of doctors is being marginalized—especially in small urban centers, where there simply isn’t enough money to allow time off for teaching.

JDT: Why was so much more teaching possible in the good old days?

RMB: Medical wages and salaries were so much lower then. In the ’60s, hospitals paid less than 50 cents per hour to the custodians and laundry workers. I received $2,200 for an entire year as an intern and $3,300 as an early resident. Now salary costs alone make the delivery of good care unaffordable.

JDT: Speaking of those days, what made you into an ophthalmologist?

RMB: I went to a big public high school in Bridgeport, Connecticut, where a low percentage of students went on to graduate from college. I was always quite adept at math and science. My father wanted to be an aeronautical engineer. Like most immigrant boys at that time, he did not have funding to afford schooling. So he made his career in business. But I knew my father wanted me to be the aeronautical engineer he couldn’t become. With encouragement from him and my high school principal, I was accepted at Massachusetts Institute of Technology (MIT).

JDT: What happened at MIT?

RMB: At 11 o’clock one night near the end of my first year, I was struggling over some technical drawings of a Japanese fighter plane. I said to myself, “if you have to do this for the rest of your life, you’ll be crazy.”

JDT: So you got out of aeronautical engineering?

RMB: Yes, after some searching, I settled on “quantitative biology.” Graduation at MIT required the writing of a thesis. At this point, I was fortunate to meet J. Y. Lettvin, MD, PhD, a boarded neuropsychiatrist. He eventually invited me to join his laboratory. Good science was the result.

JDT: What happened when you met Jerry Lettvin?

RMB: I walked into his lab, a desperate third-year student, looking for a thesis advisor. Sitting around this genius were the likes of Pitts and McCollough. People were exchanging ideas on life as well as science. That laboratory group changed my life by providing a rich milieu in which I could begin intellectual growth. This is where Sharon comes in. We had been dating since high school and her dad was an ophthalmologist. Going


through my father-in-law's books I found a copy of Polya. I became intrigued by the ratio—1:1 of midget bipolar cells to single cell receptor. So I went back to see Dr. Lettvin and on the basis of that small obsession of mine, he invited me to join his laboratory for a senior thesis.

JDT: You had never done anything like this before. How did you know what to do?

RMB: I stumbled a lot, but Lettvin's hand and others were there to help. Jerry was always presenting questions that could be answered and one day he announced that Dr. Axelrod and I would demonstrate how cockroaches smell. After working for a month, the day had arrived and we had not been successful. I suggested that we cut the tip off one of the hair cells on the antennae. Jerry took a big, long drag on his short Camel and all of the sound amplifiers hooked to the cockroach antenna went off. We had developed a new system for studying smell in cockroaches.

JDT: So you were off on a career in basic science.

RMB: No, I went to medical school.

JDT: Why?

RMB: I wanted to combine service with science. Jerry wanted me to get a PhD in neurophysiology from Humberto Maturana, PhD, in Chile. Sharon and I were getting married, and Jerry sent two of his buddies to convince my parents and my future in-laws to let me go off to Chile. I went off to Jefferson Medical College (Philadelphia) instead.

JDT: And at Jefferson?

RMB: I quickly ran into difficulty with laboratory attendance especially in histology. Students were mandated by the Commonwealth of Pennsylvania to spend a certain amount of time in the laboratories, but I got the work done in half the time allotted, so I would go off to the library to study. The Dean called me in to his office. He told me that there was no legitimate excuse for skipping lab time. This is where my second mentor came in—Al Sedar, PhD, an electron microscopist. Working for him in my second year, I second-authored (with him) two papers that still stand as classics on succinic dehydrogenase systems in bacteria (J Cell Biol 1965;24:285-295; J Cell Biol 1965;27:53-66).

JDT: Didn't that kind of success make you feel comfortable as a basic scientist?

RMB: Yes, but I still felt the tug of service. And my father-in-law was an ophthalmologist and a great role model. By this time our first child was born. I applied for an ophthalmology residency.

FIG. 6. Neuro-ophthalmology Faculty, Washington University, 1975, with former fellows Lenore Breene (left), Terry Klingele, and Bill Hart.

FIG. 7. Neuro-ophthalmology Faculty, Washington University, 1987, with fellow Tom Slamovits.

JDT: Did you have any idea at that time that you’d end up in neuro-ophthalmology?
RMB: Not really. In retrospect, I was influenced by an exciting exposure to neurology and neuro-ophthalmology rounds in medical school and internship at Jefferson.

JDT: How did you choose your ophthalmology residency?
RMB: I was ready to go back to Connecticut—to Yale, but I also applied to Washington University (in St. Louis).

JDT: Why consider Wash U, in the middle of the country?
RMB: It had a great reputation for having smart residents. My father-in-law urged me to apply there.

JDT: Did you apply anywhere else?
RMB: No. I met Mort Smith, MD, who was spending 2 years in Washington, DC, at the AFIP (Armed Forced Institute of Pathology) between the end of his third and beginning of his chief residency year at Wash U. He was interviewing candidates for the ophthalmology residency at Wash U. He offered me a position and I took it.

JDT: Without first going to St. Louis?
RMB: Yes.

JDT: The power of Mort Smith. What was it like as a resident in St. Louis in those years (1965–1968)?
RMB: Exciting, nurturing, dynamic. Dr. Becker (Bernard Becker, MD, Chair of Ophthalmology)—the third mentor in my life—set standards of excellence I have tried to emulate all my life.

JDT: How did you get in neuro-ophthalmology?
RMB: As a first-year resident, I went on field trips to southern Missouri to examine rural, indigent patients. On the first one of those trips, I went with a senior resident who had written a paper on paradoxical pupillary responses with Andrew Gay, MD (then head of the neuro-ophthalmology section at Wash U). He asked me to look at it, and I ended up rewriting the paper. Andy was impressed enough to offer me an opportunity to co-edit an edition of *International Ophthalmology Clinics* (1967;7) dealing with neuro-ophthalmology. The next thing I knew I was a fellow in neuro-ophthalmology under Andy. Then I spent another year in St. Louis as a glaucoma fellow. Halfway through that year, Andy came to tell me that he was leaving to go into private practice in Maine. Becker and Gay asked me to take over the neuro-ophthalmology service and I accepted.

JDT: Did you accomplish any science while you were in St. Louis?
RMB: Yes. Dr. Becker always found a way to support our work on establishing the anatomy of the pupillary pathways in rats, cats, and monkeys (*Brain Res* 1982; 249:379, *Brain Res* 1982;261:303, *Brain Res* 1983;101:930). He was my intellectual father. He encouraged us to be eclectic and independent in our scientific interests.

JDT: And you weren’t hounded to see more patients?
RMB: No, that pressure did not start until the late ’80s, but even so, we (Bill Hart, Terry Klingle, and I) vastly increased the clinical volume of the neuro-ophthalmology service.

JDT: Did you have neuro-ophthalmology fellows?


JDT: What made you decide to become a department chair?

RMB: I had always wanted to run my own program. I couldn’t resist the offer to come back to the East Coast, to an urban but underserved area, to a program previously run by my old friend Paul Henkind (Chair, Department of Ophthalmology, Albert Einstein College of Medicine, until 1988).

JDT: How do you feel about that experience?

RMB: Good. As I said earlier, I feel I’ve accomplished some goals, but the battles have been tough.

JDT: As you look back, which part of your career are you going to remember most?

RMB: The book (Burde, Savino, and Trobe: Clinical Decisions in Neuro-ophthalmology, 1st ed., 1986; 2nd ed., 1993. Philadelphia: Mosby). I’m not just saying this for you and Peter (Savino). When we started making up the decision trees, it nearly drove me mad. Turning everything upside down, going from symptoms and signs to conditions instead of the usual way, from conditions to their symptoms and signs. In the early 1980s, few other writers were presenting material in a learning tree format. I remember the arguments the three of us had—your telling me that no one else in the sane world approached patients the way I did. But we all survived the experience, and we’re even closer for having done so. The book changed the way we thought about neuro-ophthalmic patients. Decision trees are the best way I know of to bring science into the service of patient care. You know, being a true physician, not just a good doctor.
Neuro-Ophthalmology at Large

Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting, April 29–May 4, 2001

Alfredo A. Sadun, MD, PhD, Mark J. Kupersmith, MD

More than 5,000 abstracts were presented at the 2001 Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting, Fort Lauderdale, FL, April 29–May 4, 2001 (Invest Ophthalmol Vis Sci 2001;42 (4). We highlight some of the investigations of interest to neuro-ophthalmologists. Abstracts are referenced by number (#), sections, and symposia by the letter S.

Apoptosis and regeneration

The week began with two symposia, one devoted to molecular mechanisms of apoptosis and cytoprotection and the other to tissue injury, repair, and regeneration. The first symposium was dedicated to Richard Lolley, PhD, former Dean of Research at the USC School of Medicine, and an important contributor to the field of the neurobiology of inherited degenerative disorders who died last year. The symposium reviewed how mouse mitochondrial mutant strains owing to a mitochondrial genome knock-out are used to investigate mitochondrial dysfunction. The pathophysiology of these disorders goes beyond that of energy deficiency to involve problems with reactive oxygen species and the early initiation of apoptosis. In the second symposium, investigators described how cultured neural stem cells are implanted in the mature nervous system to facilitate regeneration. The implantation of these stem cells leads to interactions whereby the host tissues modify the stem cells. Stem cells cause release of factors and alteration of the mature nervous system (S1). Stem cells release factors that alter the environment and interaction with other stem cells and mature neurons.

Cataract and color vision

Nuclear opacification of the crystalline lens is correlated with color vision loss owing to selective wavelength absorption (S7).

Axonal imaging

Imaging of the optic nerve and the peripapillary nerve fiber layer has improved with technical advances but is still limited in the precise longitudinal analysis of axonal loss. Media clarity, corneal birefringence, an intraocular lens, and ocular movement are confounding factors (S15–S19). The GDx nerve fiber analyzer may not recognize nerve fiber layer swelling when caused by ischemia (#110).

Eye movements

The neural control of eye movements was reviewed in a mini-symposium (S11). The superior colliculus appears to be important in providing a motor map for sequential saccades. Target distance modulates the vestibuloocular reflex. Three short-latency mechanisms normally compensate for subject movement to maintain fixation before the subject is aware of a disturbance in vision.

Neuroprotection

Aspects of the molecular regulation of nitric oxide synthase 2 expression in astrocytes in the optic nerve head were demonstrated and associated with a number of cellular signals and cytokines (#128). In a rat model of retinal ischemia (high intraocular pressure), systemic administration of brimonidine was more effective than topical administration in mitigating the extent of retinal ganglion cell (RGC) drop out and electroretinogram (ERG) abnormalities (#130). However, as in previous models of central nervous system ischemia, a beneficial effect required that brimonidine be administered at least 1 hour before onset of ischemia. The administration of brain-derived neurotrophic factor could mitigate RGC death after crush injury to the optic nerve in rats (#132). A similar experiment demonstrated the utility of the trophic factor CTNF (#134). The glial-derived neurotrophic factors (GDNF) and glomerular filtration rate (GF-Ralph-1), as well as neurturin and brain-derived neurotrophic factor (BDNF), have receptors located on RGCs; these receptors become apparent after axotomy in the rat (#138). Because these are separate receptors, their trophic effects may be additive. A different type of study (#141) demonstrated the neuro-
protective effects of memantine in two types of rat models of RGC injury: optic nerve crush injury and RGC ischemic injury through induced intraocular hypertension.

**Multifocal ERG**

Two months after optic nerve section, the multifocal ERG is unchanged from controls, suggesting RGCs make little or no contribution to this signal (#786).

**Frequency doubling perimetry**

The danger of accepting new technology uncritically was highlighted in a study showing that frequency doubling time (FDT) perimetry was poor at detecting the visual field defects of brain lesions, especially in the posterior visual pathways (#807). FDT detected fewer than 50% of the quadrantanopic defects detected by Humphrey 24-2 testing. The sensitivity of FDT perimetry can be improved by offsetting the stimulus by 3 degrees from the vertical meridian (#820).

**Retinal ischemia**

In mice developed with N-methyl d-aspartate (NMDA) receptor subunit knock-out, experimentally induced transient ischemia caused significantly less RGC death than it did in controls, which suggests excitatory amino acid-related injury acts through these receptors (#1055).

In a patient with antiepileptic antibodies, a central retinal vein occlusion developed despite the patient’s being already treated with warfarin (#1270).

Retrograde axonal flow can be demonstrated by careful ophthalmoscopy in retinal artery occlusion. In these cases, swelling and opacification similar to cotton wool spots can be seen. This phenomenon probably accounts for some of the swelling of the optic disk seen with central retinal artery occlusion (#1281).

An intravenous treatment of 50 mg rt-PA followed by eight days of heparin treatment improved the vision in three patients with macula-involving branch artery occlusion of less than 12 hours’ duration (#1296).

**Gene therapy**

A mini-symposium discussed progress in gene therapy and the issues facing future development (S302). In a canine model of Leber’s congenital amaurosis, the known deleted gene was transfected into three animals using a methodology that not only got the gene into the retinal cells, but altered the promoter region of the existing genes. A functional gene resulted, as evidenced by a demand for a high-energy supply (#1624).

**Retinal ganglion cells**

A mini-symposium on RGCs discussed how glial cells, which provide the normal supportive environment for neurons, can become a destructive influence when reactive astrocytes evolve (S305). The Müller glial cell is particularly important in maintaining RGC function. The notion of selective loss of parvocellular RGCs in early glaucoma was demonstrated to be erroneous.

**Congenital nystagmus**

Increased foveation time followed horizontal rectus tenotomy in 10 adults with congenital nystagmus. Binocular visual acuity improved by five letters or more in three subjects (#1720).

**Leber’s hereditary optic neuropathy**

In a Leber’s hereditary optic neuropathy (LHON)/11778 pedigree with 80 members and six generations, environmental factors—particularly tobacco, alcohol, and toxic exposures—increased the disease expression (#1754). Furthermore, this susceptibility to environmental factors was increased in the subset with haplo group J. More than two thirds of 44 patients visually impaired by ethambutol toxicity showed dramatic recovery, but recovery was less likely in older patients (#1755).

**Intracranial hypertension**

Immunofluorescent antibody studies revealed somatostatin receptors on arachnoid granulation and choroid plexus cells. These receptors might play a role in the iatrogenically induced increased intracranial pressure after growth hormone therapy (#1762).

**Giant cell arteritis**

In a series of patients with giant cell arteritis treated with corticosteroids, reduction of the prednisone dose to 40 mg daily by the fourth week of therapy had a low a rate of drug complications and only one recurrence of giant cell arteritis symptoms. In this single instance, increasing the prednisone dose reversed the symptoms (#1765).

**Goldfish axons**

In actively growing goldfish optic nerve axons, mitochondria migrate toward the growth cone, possibly owing to a demand for a high-energy supply (#1779).

In an elderly patient with LHON/3460, there was depletion of Purkinje cells largely limited to the superior cerebellar vermis (#1781). This depletion may reflect the cellular architectural and surface antigen homology between RGCs and Purkinje cells.

**von Hippel-Lindau**

Genetic testing for the von Hippel-Lindau gene was negative in 10 patients with an isolated retinal capillary hemangioma, which suggests that this test could be used to screen patients for the complete disorder (#1807). New retinal hemangioblastomas developed in 22% of eyes of 68 patients with the von Hippel-Lindau gene over a median follow-up period of 16 months (#1808).

**Functional MRI**

Functional MRI (fMRI) was used to demonstrate that stereopsis is dependent on a network of functional fields found in the occipital, parietal, and prefrontal cortex regions (#2160). Single fMRI studies inconsistently demonstrated the retinotopic mapping of the V1-V2 border. Signal averaging of repeated measures is necessary to accomplish this (#2192). The voxel (three-dimensional pixel) size needs to be optimized and is an important parameter in detecting brain activation in fMRI with T2-weighted echo-planar imaging (#2197).
MRI coordinates
A new method for specifying cortical location on MRI used a coordinate system with the fundamental axis in the sagittal plane extending from the anterior corpus callosum to the posterior aspect of the parietooccipital sulcus. This system seemed to be easier to use than previous systems (#2193).

Optic nerve injury
The RGC biologic basis for ischemic injury and neuroprotection was reported. Glutamate-nitric oxide signaling during development may influence the circuitry between RGCs, amacrine cells, and bipolar cells (#2025). Schwann cell-derived neurotrophic agent, administered intraocularly, can protect RGCs from optic nerve crush injury (#2035). Nitric oxide plays a major role in retinal damage after ischemia/reperfusion injury in the rat (#2211). This observation fits well with the report that inhibiting nitric oxide synthase with aminoguanidine partially protected the optic nerve axons after ischemia injury from increased intraocular pressure in the rat eye (#2224).

Glaucma
In an experimental unilateral glaucoma monkey model, the lateral geniculate nucleus developed atrophy not only in layers with connections to the glaucomatous eye, but also in layers receiving input from the unaffected eye. This finding suggests a more complex relationship for glaucomatous progression than merely injury at the ganglion cell level and that still unclear central mechanisms play a role (#2212).

“Filling in”
The perceptual completion effect (“filling in”) in a patient with an occipital injury and hemianopic scotoma was demonstrated to be a retinotopic phenomenon and not attributable to inattention (#2776). Completion of filling in also occurs within the scotomas of age-related macular degeneration. Modeling that enlarges the receptive fields of adjacent normal retina appears to account for some of the observed improvement in the field defect, including retention of pattern detection (#2777).

Retinal bipolar cells
A mini-symposium reported that the bipolar cell is the starting point for parallel processing of vision (S519). On bipolar cells have sustained or transient responses as well as on or off responses. These functions are modulated through subtypes of γ-aminobutyric acid receptors. Multiple types of bipolar cells, each with unique axons, provide the basis for complex interactions with photoreceptor input and interaction with amacrine and ganglion cells. Amacrine cells might provide the modulation that results in differential tuning of bipolar cells.

Parkinson’s disease
Parkinson’s disease causes saccadic multistepping worse with upward saccades. L-dopa significantly reduces this dysfunction (#3355).

Histology of ischemic optic neuropathy
In a well-preserved histopathologic specimen of an optic nerve that had had anterior ischemic optic neuropathy 20 days pre-mortem, there was severe axonal loss but no evidence of an infarct in a single vascular territory (#3360).

Post-operative ischemic optic neuropathy
In a retrospective survey by anesthesiologists of 27 patients with postoperative anterior or posterior ischemic optic neuropathy, visual loss after spinal or cardiac surgery was associated with low intraoperative blood pressure and/or hematocrit, vigorous fluid management to maintain perfusion of the ocular tissues, and patient positioning (#3363).

Leber’s congenital amaurosis
Numerous investigators reported progress in uncovering genetic defects in Leber’s congenital amaurosis (S640, S644–645).

Brimonidine
Brimonidine mitigated the apoptosis induced by tumor necrosis factor (TNF) on retinoblastoma cells in culture, but only in the faster dividing cell lines (#3557). The same dose of brimonidine caused death of some of these cells. Curiously, TNF in conjunction with brimonidine led to less cell death, proving that two wrongs sometimes make a right.

Pupils and retinal ganglion cells
A morphologically distinct RGC type mediated the pupillary light reflex in rhinoceros monkeys (#3639). This finding has interesting clinical implications, explaining perhaps why the pupillary reflexes are spared in some optic neuropathies (see #5020 below).

Thrombolysis of retinal vein occlusion
Direct cannulation of the retinal venous system with infusion of rt-PA via a pars plana approach with vitrectomy was performed in approximately 60 patients with central retinal vein occlusion, most of whom had prolonged reduction central acuity beforehand. The authors claimed three-line improvement in more than 50% and no major complications. Vitreous hemorrhage occurring two months after the procedure cleared spontaneously. One retinal detachment that did not affect the macula was surgically repaired (#3860).

Retinal ischemia
Adenosine A2a and A1 receptors were increased in the inner nuclear layer of the retina six hours after ischemia induced by 45 minutes of elevated intracocular pressure. The A1 receptor is predominantly expressed on ganglion cells; the A2a receptor is predominantly expressed in the nerve fiber layer and ganglion cell layer (#3986).

In a primate model of transient central retinal artery occlusion induced by clamping the CRA for 190 minutes, vitreous sampling failed to demonstrate the expected elevation of glutamate or glycine (#3986).

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Pre-treatment with carvedilol, a beta blocker that has antiapoptotic properties, and MK-801, an NMDA antagonist,

preserves more retinal function than either agent alone (#3993). Pretreatment with trimetazide, an agent used for prophylaxis of angina pectoris, reduced the effects of ischemia on retinal morphology (#3998). In vitro hypothermia (25°C) prevented a drop in adenosine triphosphate levels and reduced morphologic changes in the rat retina (#3998).

**Homocysteine toxicity**

Intravitreal administration of homocysteine appears to be toxic to RGCs; the combination of homocysteine and glutamate induces even more ganglion cell loss (#4004).

**Batten’s disease**

In a murine knock-out gene model of Batten’s disease, the optic nerve develops significant loss of axons (#4112).

**Vigabatrin**

A wide-field (57-90 degrees) multifocal ERG can demonstrate loss of peripheral retinal dysfunction in patients on long-term vigabatrin treatment (#4206).

**Pupil studies**

Topical brimonidine causes the pupil to be approximately 1 mm smaller but has no effect on the clinical determination of the pupillary response to light (#4415). A study using computerized infrared pupillography confirmed the clinical observation that a brighter light stimulus produced a greater distinction between normal subjects and patients with unilateral anterior visual pathway lesions (#4518).

**MRA and third nerve palsy**

A statistical analysis of the literature on magnetic resonance angiography (MRA) in patients with isolated third nerve palsy concluded that MRA is not adequate to rule out an aneurysm in most patients younger than 70 years. However, the authors presented no original data. Their model did not distinguish between extradural and intradural aneurysms or consider MRA that includes high-resolution techniques or review of the source image data (#4531).

**Myasthenia gravis**

If patients with ocular myasthenia gravis are treated with corticosteroids, the development of generalized myasthenia gravis at two years appears to be significantly reduced. In diagnostic intravenous edrophonium testing for myasthenia, most patients require no more than 3 mg to demonstrate an ameliorative effect on ptosis or ocular motor dysfunction (#4532).

**Optical coherence tomography**

Optical coherence tomography appears to be the best imaging technique to view the nerve fiber layer. Asymmetry analysis of comparable areas in both eyes is useful in overcoming interindividual variations (#4548).

**Rat model of ischemic optic neuropathy**

A model of nonarteritic ischemic optic neuropathy was created in rats by using a laser activating an injected photosensitizing dye to thrombose small vessels supplying the optic nerve. Pale swelling of the optic disk, reduced visual evoked potentials, and a loss of RGCs were demonstrated (#5019).

**Pupil pathways**

Histopathology using Dil, a fluorescent dye, in a patient with LHON demonstrated preservation of optic nerve input to the pretemporal region in the brain. This provides anatomic evidence for the clinical observation of relative preservation of the pupillary light response in these patients and supports the notion that some axons in the afferent loop of the pupillary reflex are not related to conscious vision (#5020).
53rd Annual Meeting of the American Academy of Neurology, May 6–12, 2001

Mark L. Moster, MD, John Guy, MD

These are a selection of papers and posters covering neuro-ophthalmology and neuro-ophthalmologic aspects of neurologic disorders that were presented at the 53rd Annual Meeting of the American Academy of Neurology, Philadelphia, PA, May 6–12, 2001 [Neurology 2001;56(suppl 3):A1–481]. The selections are arranged by topic.

**TUMORS**

A series of seven infants treated for visual pathway gliomas with chemotherapy and occasionally partial resection demonstrated similar outcomes as did older children, in contrast to prior reports that have found that infants are less responsive to treatment (Packer R, Washington, DC, P01.060).

**MITOCHONDRIA**

A new mitochondrial mutation at site 9995 was found in an Iraqi Jewish family with optic atrophy and dystonia (Brown MD, Atlanta, GA, P02.091).

**VISUAL FIELDS**

Sita-Fast Humphrey perimetry is as reliable as Goldmann Perimetry in most patients with severe (20/200 or worse) visual loss or severe neurologic deficits (Szatmary G, Atlanta, GA, S06.002).

**INTRACRANIAL HYPERTENSION**

1. Twelve patients with idiopathic intracranial hypertension occurring during pregnancy responded well to treatment with weight control and lumbar punctures (when necessary); acetazolamide was not necessary for control (Kupersmith M, New York, NY, S06.003). 2. Cerebrospinal fluid pressure monitoring for an average of 1.9 days was helpful in establishing the diagnosis of pseudotumor cerebri in patients without papilledema (Williams MA, Baltimore, MD, P02.146).

**EYE MOVEMENTS**

1. Two patients had loss of saccadic eye movements after cardiac surgery without magnetic resonance imaging (MRI) lesion to explain the deficit. They were disabled by inability to read or survey their environment (Stahl JS, Cleveland, OH, S08.004). 2. Patients with Machado-Joseph disease (SCA-3) had loss of the vestibulo-ocular reflex, helping to distinguish this disorder clinically from patients with other spinocerebellar ataxic syndromes (Gordon CR, Kfar Saba, Israel, S08.003). 3. In SCA-7, slowing of voluntary saccades was seen even in patients with subclinical disease (OH AK, Los Angeles, CA, P01.044). 4. Presymptomatic gene carriers of Huntington's disease had abnormalities in saccadic function, OKN gain, and pursuit (Blekher TM, Indianapolis, IN, P01.101). 5. MRI in progressive supranuclear palsy (PSP) showed mesencephalic atrophy, fourth ventricular enlargement, increased signal in globus pallidus and putamen, and increased interpupillary angle (Rolland Y, Rennes, France P04.011). 6. A study of slow vertical saccades in PSP found that it was unlikely that this was owing to involvement of the omnipause neurons and more likely to involvement of burst neurons (Leigh RJ, Cleveland, OH, S08.002). 7. A review of 110 patients with biopsy-proven temporal arteritis found 15 (12.7%) with diplopia; five had third nerve paresis, three had sixth nerve paresis, and six had transient diplopia with a normal examination (Cornblath WT, Ann Arbor, MI, S06.005).

**LABYRINTHINE DYSFUNCTION**

1. A new bedside test of utricular function, called the "head-leave maneuver," consists of having the examiner hold the head and move it laterally with a very short, rapid excursion. Corrective saccades are seen in patients with unilateral labyrinthine hypofunction, or cerebellar disease (Zee DS, Baltimore, MD, S08.001). 2. A series of patients with "complex paroxysmal positional nystagmus" was described. This is a manifestation of benign paroxysmal postural vertigo (BPPV) involving multiple semicircular canals. These patients require more complicated treatment than do those with conventional BPPV (Fife TD, Phoenix, AZ P01.042).

**MULTIPLE SCLEROSIS**

1. The NIH VFQ-25 questionnaire is an effective measure for capture of visual loss in multiple sclerosis (MS)
patients who have a high degree of self-reported visual dysfunction (Balcer LJ, Philadelphia, PA, P01.049). 2. A 20-year follow-up study of MS patients who presented with optic neuritis (ON) or diplopia revealed that 81% of ON patients had normal visual acuity but that subtle abnormalities persisted. Those presenting with diplopia more frequently switched to secondary progressive MS with decreased visual acuity than did those with optic neuritis (Vorobeychik G, Vancouver, BC, Canada, P03.099). 3. The ONTT found that African-Americans had a non-statistically significant tendency to develop clinically definite MS at a lower rate compared with Caucasians (20% versus 32%), but African Americans who developed MS had worse visual impairment than did Caucasians (Nazarian SM, Little Rock, AR, P03.093).

VISUAL PROCESSING

1. A study of functional MRI (FMRI) in patients looking at objects displayed in non-canonical (unusual) views was compared with subjects looking at objects displayed in canonical (usual) views. During viewing of non-canonical objects, there was activation of the left occipitotemporal and right parietal cortex and a small degree of cerebellar activation (Terhune KP, Philadelphia, PA, P01.050). 2. Although form perception, face recognition, and color perception are processed by the parvocellular visual pathway, a study of two patients revealed a separation between performance on shape perception as compared with color or facial perception, providing evidence for separation of these functions in the ventral (occipitotemporal) pathway (Kim JS, Cheju, Republic of Korea, S06.004). 3. In contrast to patients with developmental (congenital) prosopagnosia, those with acquired prosopagnosia were able to perform covert processing of faces, as evidenced by their ability to recognize faces when given the name of a person to match to the face. Presumably, congenital prosopagnosia patients do not create a store of accurate facial memories in the brain (Barton JJS, Boston, MA, S35.007). 4. Two patients with acquired cerebral achromatopsia were able to perform saccades to isoluminant chromatic stimuli, which they could not see, demonstrating a sort of “blind-sight” (Celesia GG, Maywood, IL, S35.005). 5. A syndrome of transient topographic disorientation was described. Patients had transient inability to navigate through familiar environments. Five of 10 patients had recurrent episodes. Studies of single-photon emission computed tomography (SPECT) and neuropsychologic tests suggested a persistent right hemisphere dysfunction. These patients have characteristics similar to those of transient global amnesia in that they demonstrate no evidence of seizures or cerebrovascular disease (Gill-Neciga E, Seville, Spain, P01.099).

VISUAL HALLUCINATIONS

1. Visual hallucinations are considered a major feature of dementia with Lewy bodies (DLB). Forty-seven of 66 patients with DLB (72%) had visual hallucinations, most often involving images of people. Auditory hallucinations or delusions were only seen in those who also had visual hallucinations. Delusions consisted of phenomena that were related to the patients’ visual hallucinations (Ferman TJ, Jacksonville, FL, P03.044). 2. Among a cohort of 99 Parkinson’s disease patients, 29 began the study with visual hallucinations and 30 developed them during the study. Of the 29 with study-onset hallucinations, only four (14%) showed resolution. Among the 60 patients who did not have visual hallucinations at study onset, 50% developed them within 4 years. Neuropsychically rare in resolving the visual hallucinations (Goetz CG, Chicago, IL, P03.147).

MIGRAINE

Late-life migraine equivalents, such as the scintillating scotoma, showed excellent response to topiramate. Five patients over age 65 with attacks lasting from 15 minutes to 1 hour, occurring five to 14 times per week, had complete resolution within 12 weeks of treatment with an average dose of 78 mg/d (Roberson S, Nashville, TN, P01.128).

STROKE

1. The results of the multicenter Warfarin-Aspirin Recurrent Stroke Study (WARSS), comparing long-term anticoagulation to aspirin in 2,206 patients with minor stroke, showed no difference between treatment groups (warfarin only, aspirin only) in the 14 weeks of recurrent stroke and death. Both treatments were equally safe (P01.002). 2. A study of patients with spontaneous cervical artery dissections found that risk factors included recent infection, migraine, and minor trauma or exercise (Guillon B, Nantes, France, P03.002). 3. Thirty-two of 110 consecutive patients with carotid artery occlusion had ocular ischemic findings on examination and four of these patients developed severe signs of clinical ocular ischemia (Klijn CJM, Utrecht, The Netherlands, P04.113). 4. Anticoagulation for radiation optic neuropathy showed improvement in three patients, but visual details were not provided in enough detail to draw much meaning from this small series (Venkatasubramanian N, Singapore, P01.051).

EYELID

A study of Botox treatment of apraxia of lid opening provided further evidence that the benefits of Botox are explained by diminishing activity of the hyperactive orbicularis oculi. The treatment was generally effective (Boghen D, Montreal, Canada, P01.053).

TRANSPLANTATION

Based on evidence from animal models of Parkinson’s disease that intrastriatal implantation of retinal pigment epithelial cells produces benefit, a pilot study of six patients was performed. Surgery was tolerated well and initial efficacy evaluation showed promise (Watts RL, Atlanta, GA, P04.102).
Books Reviews


This is a multi-authored book reviewing basic immunology and clinical aspects of ocular immunology. The book is designed to appeal to residents and practicing ophthalmologists, although the overall tone is academic and strongly oriented toward the basic mechanisms of immunologic disease rather than emphasizing clinical management.

The first six chapters of the book deal with immunology, immunopathology, and immunoregulation with strong emphasis on these processes in the eye. There is an extensive review of the literature. The remaining 16 chapters focus on various aspects of specific immunologic diseases of the eye and orbit, including a chapter on uveal melanoma. Both infectious as well as purely inflammatory conditions are discussed. The treatment of some topics is done in significant depth, whereas others are treated in a more sketchy manner. For example, Herpes simplex keratitis is discussed in three pages, whereas in another chapter 19 pages are devoted to corneal melting syndromes such as Mooren’s ulcer.

The discussion of immunology of the eye is excellent and makes this book a good choice for ophthalmologists in training as well as those interested in ocular research. The bibliographies at the end of each chapter provide a good balance for those wishing to search for more details about the scientific studies. The chapter on orbital inflammatory disease is particularly good in its clinical relevance, as are the chapters on toxoplasmosis and Sjogren’s syndrome.

The authors of this book have chosen to underemphasize treatment and management decisions. Although the immunology underlying the disease process is important, the book is of less use to clinicians because therapy is not dealt with evenly. There is no chapter on therapeutic options for immunologic or infectious disease in which mechanisms of action and toxicity can be discussed. The chapter on sarcoidosis, for example, contains one paragraph on the treatment of ocular sarcoidosis and does not tell the practitioner anything that he or she already did not know. The chapter on ophthalmic manifestations of AIDS discusses cytomegalovirus retinitis but does not discuss the various advantages of the therapeutic options that are available. Intravenous ganciclovir and foscarnet are discussed. Cidofovir and ganciclovir implants are mentioned in passing, but there is no discussion of Vitrawene or oral ganciclovir. In addition, there are no chapters on inflammatory disease of the optic nerve or on immunologic disease, such as myasthenia gravis, which affects ocular structures, so the neuro-ophthalmic community will be disappointed.

This text can be useful for residents and research-oriented ophthalmologists as well as non-ophthalmologists who are interested in immunologic effects in the eye. The book deals well the ACAID immune privilege phenomena in the eye, and this will be of interest to nonocular immunologists.

The introduction suggests that the clinician-reader will find this book to be useful—it is very useful in its discussion of immunologic mechanism of ocular disease. It is not likely that a clinician would turn to this book for the diagnosis, treatment, or management of an inflammatory ocular disease. The introduction makes it clear that the authors understand that current immunologic theory and knowledge “has not, as of yet, led to major transformations and improvements in the treatment of ocular inflammatory disease.”

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This is a scholarly and detailed historical description of medical education in the United States in the twentieth century. It chronicles American medical education from the turn of the century to the era of managed care.

This book will do for the twenty-first century what the Flexner Report did for the twentieth century. It will become the definitive academic work on medical education and medical schools for the next several decades. Detailed and annotated, it reads like good novel.

The book is divided into three sections. The first section is Fulfilling the Social Contract: Medical Education as a Public Trust and the Capture of Public Confidence. Here it relates the movement from proprietary to university-based training in medicine, chronicles the impact of major philanthropists on structuring medical education, and traces the relationship of the medical school to its association with larger universities. Dr. Ludmerer outlines the growth and rise of the formal teaching hospital and defines the contract between society and postgraduate medical education. This section outlines the practical apprenticeship of seeing, teaching, and doing and shows us how the system that we take for granted came to be.
The second section is entitled Medical Education in the Era of the Multiversity: The Growth of Research and Service in a Period of Abundance. It relates the golden years of medical education, the ascendancy of research, the expansion of clinical demands on faculty, the maturation of the graduate medical education curriculum, and the changing roles and behavior of medical students.

The last section is entitled “Breaking the Social Contract: The Erosion of University Values, the Decline of Public Spiritedness and the Beginning of the Second Revolution in Medical Education.” It characterizes the impact on graduate medical education of Medicare, Medicaid, civil rights changes, and the enormous financial pressure under which academic health centers have been placed. It ends in a provocative chapter entitled “A Second Revolutionary Period.” Dr. Ludmerer characterizes this as a time of the erosion of the clinical learning environment, the diminishing of faculty scholarship, and the reemergence of the proprietary system of medical schools in which the faculty’s financial aids take priority over education and research.

This is a balanced, meticulously researched literary history of American medicine and its educational upheavals. It is wonderfully written, easy to read, and, although not answering the questions, raises them. It is a wonderful description of the world in which we work and indeed the world in which we live.

The only deficiency of the text is that the reader misses more specific goals and directions about where medical education should be going; having done all the research involved and thought about the issues so compellingly, one wants to ask Dr. Ludmerer for some advice here. Understandably, this was not the intent of his treatise; nonetheless, it is a summary that would complement.

All of us who are doctors, all of who work in academic health centers, and all of us who are involved with students and residents will find this an interesting narrative of medical education in the twentieth century. It will undoubtedly be the foremost document upon which twenty-first century education will be structured.

Dr. Ludmerer is a respected medical educator, as well as a professor of medicine at the Washington University School of Medicine. His book will provide the background for making educated choices about the future of medical education in the coming years. Read it.

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Ankylosing Spondylitis in a Case of Recurrent Optic Neuritis

A 20-year-old man presented with sudden diminution of vision OD in February 1997. Examination revealed a visual acuity of light perception OD and 20/20 OS with a relative afferent pupillary defect OD and a normal fundus. The intraocular pressures and slit-lamp examination in both eyes were also unremarkable. With the provisional diagnosis of retrobulbar neuritis OD, the patient was examined. He had mild anemia (-Hb 11 gm%), an erythrocyte sedimentation rate (ESR) of 5 mm (Wintrobe), normal urine, and normal chest and paranasal plain x-rays. Indirect hemagglutination (IHA) for toxoplasma was negative and VDRL was nonreactive. Blood cultures showed no growth.

The visual evoked response showed increased latency and decreased amplitude in the OD. Brain magnetic resonance imaging study was not suggestive of multiple sclerosis or any other neurologic abnormality.

The patient was given 1 g methylprednisolone in 5% dextrose intravenously for 3 days followed by 60 mg oral prednisolone once daily for 10 days in a tapering dose. By the third day of intravenous methylprednisolone treatment, visual acuity OD improved to 20/30. Six weeks later, he returned with recurrent retrobulbar neuritis OD, which was again treated with the same regimen.

In November 1998 and June 1999, he presented with similar recurrent attacks of optic neuritis OS. He was again treated with the same regimen.

In June 1999, the patient complained of some stiffness of the neck and lower back. He was referred to the rheumatology clinic where inflammation of the back, lumbar motion limitations, and limited chest expansion were detected. On examination, the white blood cell count was 10,200 mm^3, hemoglobin was 10.5 g/dL, ESR was 53 mm (Wintrobe), and C-reactive protein was 8.70 mg/dL (normal, <0.5 mg/dL). Rheumatoid factor and antinuclear antibodies were negative, whereas HLA-B27 was positive. Plain x-rays of the lumbar spine and sacroiliac joint showed minimal bilateral sacroilitis and syndesmophytes. He was diagnosed as having ankylosing spondylitis and was treated with 75 mg slow-release indomethacin once daily.

To the best of our knowledge, this is the first reported case of bilateral optic neuritis and ankylosing spondylitis. Optic neuritis and multiple sclerosis are known to be associated (1), and a relationship between ankylosing spondylitis and multiple sclerosis has been reported (2). Therefore, there is a possibility of incipient multiple sclerosis in our case.

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REFERENCES

Pseudotumor and Sleep Apnea

Kesler et al. (1) reported 18 male patients with pseudotumor cerebri (PTC) and compared them with 116 female patients with PTC. These authors found that the clinical features were identical in male patients compared with female patients. There were significantly fewer overweight patients (25%) in the male group, however, than in the female group (78%). The authors listed several associated factors in the male patients (e.g., hypertension, smoking, high cholesterol). Purvin et al. (2) noted papilledema in four patients with sleep apnea syndrome. I have also been impressed by several cases of sleep apnea in our male patients with PTC. I was wondering if the authors looked at sleep apnea as an associated condition in the male versus female groups in their study.

Andrew Lee, MD
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REFERENCES

Author’s Reply

We thank Dr. Lee for reminding us that the association of sleep apnea and IIH is documented. However, sleep apnea was not documented in any of our IIH patients.

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Y. Goldhammer, MD
N. Gadoth, MD
Kfar Saba, Israel
Calendar

This calendar provides a list of upcoming meetings (through May 2002) that may be of interest to neuro-ophthalmologists:

September 30–October 5, 2001
American Neurological Association
Hyatt Regency
Chicago, IL
http://www.aneuroa.org/annual.htm
Contact: (952) 545-6284 or
lorijanderson@msn.com

November 10–15, 2001
Society for Neuroscience
San Diego Convention Center
San Diego, CA
Contact: (202) 462-6688

November 11–14, 2001
American Academy of Ophthalmology (AAO) Annual Meeting
New Orleans, LA
http://www.aao.org/aaoweb1/Meetings/132.cfm
Contact: Meetings & Exhibits Division, (415) 561-8500, ext. 320

February 9–14, 2002
Frank B. Walsh Meeting

February 10–14, 2002
Copper Mountain Resort
Copper Mountain, CO
http://www.nanosweb.org/meetings/
Contact: (505) 856-9220

April 13–20, 2002
American Academy of Neurology (AAN) Annual Meeting
Denver, CO
http://www.aan.com
Contact: (651) 695-1940

April 21–26, 2002
29th International Congress of Ophthalmology
Sydney, Australia
www.ophthalmology.aust.com
Contact: +61 2 9241 1478

May 5–10, 2002
The Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting
Greater Fort Lauderdale/Broward County Convention Center
Fort Lauderdale, FL
http://www.arvo.org/meetgrid.htm
Contact: (240) 221-2900

May 5–10, 2002
International Neuro-Ophthalmology Society
Sheraton Buenos Aires Hotel & Convention Center
Buenos Aires, Argentina
Contact: inos2002@congresosint.com.ar