EDITORIAL
187 Neurosarcoidosis: How Good Are the Diagnostic Tests?
Joseph P. Lynch III

ORIGINAL CONTRIBUTIONS
190 Sarcoidosis of the Anterior Visual Pathway: 24 New Cases
Larry P. Frohman, Medhat Guirgis, Roger E. Turbin, and Leonard Bielory

198 Latent Nystagmus and Acquired Pendular Nystagmus Masquerading as Spasmus Nutans
Jaeil I. Kim, Louis F. Dell’Osso, and Elias Traboulsi

204 Visual Outcome in Eyes With Asymptomatic Optic Disc Edema
Yehoshua Almog and Michaela Goldstein

208 Pituitary Apoplexy Causing Optic Neuropathy and Horner Syndrome Without Ophthalmoplegia
Robert K. Shin, Brett L. Cucchiara, David S. Liebeskind, Grant T. Liu, and Laura J. Balcer

PHOTO ESSAY
211 Irreversible Blindness Due to Multiple Tuberculomas in the Suprasellar Cistern
Kumudini Sharma, Sanil Pradhan, Atul Varma, and Bharti Rathi

THE SECOND HOYT LECTURE
213 The Vitality of the Pupil: A History of the Clinical Use of the Pupil as an Indicator of Visual Potential
H. Stanley Thompson

STATE OF THE ART
225 The Multifocal Electoretinogram
Donald C. Hood, Jeffrey G. Odel, Candice S. Chen, and Bryan J. Winn

NEURO-OPHTHALMOLOGY AT LARGE
236 127th Annual Meeting of the American Neurological Association, New York, New York, October 13–16, 2002

(continued on next page)
Neurosarcoidosis: How Good Are the Diagnostic Tests?

Joseph P. Lynch III, MD

In this issue of the Journal, Frohman et al. (1) report 24 patients with anterior visual pathway (AVP) sarcoidosis and emphasize that sarcoidosis is frequently not recognized at presentation. They contend that a strong presumptive diagnosis of sarcoidosis usually can be established without having to perform biopsies of optic nerves or intracranial sites. Here is their evidence:

Among the 17 patients in whom the diagnosis of sarcoidosis was not known at the time of presentation, all had an abnormality on at least one of five diagnostic tests: serum angiotensin converting enzyme (SACE), chest radiograph, gallium-67 citrate (Ga-67) scan, brain magnetic resonance imaging (MRI), and lumbar puncture (see their Table 4). All but two patients had abnormal results on more than one of these tests. In one patient (Patient #5), only SACE was abnormal; in patient #15, only the Ga-67 scan was abnormal; lumbar puncture was not performed in either patient. Seven patients had abnormalities on three tests; 10 had abnormalities on four.

Based on my experience and the reports of other series dealing with neurosarcoidosis, their yield from noninvasive diagnostic tests appears relatively high. But when these tests are combined with bronchoscopy or mediastinoscopy, it should be possible to reach a diagnosis in most cases without having to resort to intracranial biopsy.

AVP sarcoidosis is a subset of neurosarcoidosis, a variant that afflicts 5% to 18% of patients with sarcoidosis (2–6). Seventh nerve palsy is the most common focal manifestation, occurring in up to 50% of patients with neurosarcoidosis (3,4,6,7). Eighth nerve palsy may be next most common, but it is often unrecognized by the patient. AVP involvement probably ranks third, comprising 15% of cases of neurosarcoidosis. Other neurological intracranial manifestations include headache, encephalopathy, stroke, seizures, hydrocephalus, focal mass lesions, involvement of the pituitary or hypothalamus, and myelopathy (3,4,6,7).

Histologic diagnosis of the intracranial lesions is difficult due to their relative inaccessibility and the potential morbidity associated with biopsy. Fortunately, more than 80% of patients with neurosarcoidosis have manifestations outside the cranial cavity, but they may be occult. In three series of neurosarcoidosis, non-neurologic involvement was noted in 94% (67 of 71) (7), 83% (29 of 35) (8), and 100% (24 of 24) (9) of patients. In two large series, intracranial biopsy was necessary in only 8% (6 of 71) (7) and 18% (12 of 68) of patients (4). Unfortunately, studies assessing the sensitivity and specificity of various clinical, radiographic, or serological studies in patients with suspected ocular or CNS sarcoidosis are rudimentary. Here is a comparison of the results of Frohman et al. (1) and other investigations.
1. Serum ACE concentrations were elevated in 16 of 21 (76%) patients in this series (1). In two other series of neurosarcoidosis, elevated SACE levels varied from 24% (12 of 51) (4) to 65% (11 of 17) (8) of patients.

2. Ga\textsuperscript{67} scans demonstrated increased uptake in salivary glands or lung in 93% of patients in this series (1). Importantly, Ga\textsuperscript{67} scans were abnormal in all 10 patients with no known history of sarcoidosis at the time of the visual loss. But in two other series of neurosarcoidosis, the reported sensitivity of Ga\textsuperscript{67} scans was considerably lower: 57% (4 of 7) (8) and 45% (14 of 31) (4).

3. Chest radiographs were consistent with sarcoidosis in 72% of patients in this series (1). Other investigators have found abnormal chest radiographs consistent with sarcoidosis in as many as 71% (25 of 35) (8) and as few as 31% (21 of 68) of patients (4). Chest computed tomographic (CT) scans are more sensitive for sarcoidosis and may be helpful in patients with normal chest radiographs (10).

4. Lung and mediastinal biopsy were infrequently performed in this series (1) but are often rewarding in patients with neurosarcoidosis (11). Bronchoscopy has a diagnostic yield of 60% to 97%, according to the number of biopsies and radiographic stage of the disease (12). One study of patients with neurosarcoidosis cited a positive yield in 59% (11 of 17) (8). When hilar lymphadenopathy is present \textit{without} lung parenchymal infiltrates, yields are 60% to 85%. Higher yields may be expected when lung infiltrates are present (12); they should be lower when patients have normal chest radiographs, but there are no published data on this point. Mediastinoscopy has a higher yield than bronchoscopy in patients with hilar or mediastinal adenopathy, but it is more invasive, expensive, and has increased morbidity (including keloid formation). Therefore, mediastinoscopy should be reserved for patients with intrathoracic lymph node enlargement \textit{and} negative bronchoscopy.

5. Brain MRI was positive in 70% of patients in the current series, showing thickening and enhancement of the optic nerve and cranial base meninges. These findings are similar to previous reports (6,9), but they are nonspecific and may occur in myriad infectious and neoplastic diseases (6).

6. Lumbar puncture revealed a lymphocytic pleocytosis or elevated protein in 88% of patients in this series (1). Others have reported elevations in CSF protein or leukocytes in 70% to 73% (4). However, these CSF abnormalities tend to be mild and utterly nonspecific (4,6,8) and do not reflect the course or severity of neurologic involvement.

7. Electromyography/nerve conduction tests (EMG) (8), the Kveim skin test (4), and biopsies of skin, conjunctiva, lacrimal glands, upper respiratory tract mucosa, liver, or muscle (4,8) often are applied to the diagnosis of occult sarcoidosis. EMG is uncomfortable and its sensitivity is likely to be low in the absence of localizing findings. The Kveim test involves intradermal inoculation of sarcoidal splenic tissue and biopsying the site of induration 5 to 6 weeks later to document granulomas (4). In neurosarcoidosis series, positive Kveim tests have been noted in 85% (41 of 45) (4) and 40% (2 of 5) of patients (8). However, the Kveim test is available in only a few centers worldwide, is not standardized, and results are not available for several weeks. Given these limitations, it has been supplanted by other techniques. Biopsies of conjunctiva or lacrimal glands have substantiated the diagnosis of sarcoidosis in 10% to 55% of patients (5,13), but the yield is low in the absence of visible nodules. Muscle biopsies have shown non-necrotizing granulomas (NNG) in 25% to 50% of patients with sarcoidosis, particularly when arthralgias, erythema nodosum, or fever are present (5). However, muscle biopsies are uncomfortable and the yield is not known in patients without muscle symptoms or signs. NNG have been noted in 21% to 97% of patients with sarcoidosis who had percutaneous liver biopsies (5). However, yields are likely to be low in the absence of specific liver findings. Because liver biopsies have potential morbidity, they should be considered \textit{only} in patients with abnormal liver function tests or hepatic enlargement or low attenuation hepatic lesions on CT.

Mindful of these data, I recommend the following approach to the diagnosis of suspected AVP sarcoidosis. When \textit{clinically evident} superficial lesions are present, such as conjunctival or cutaneous nodules or enlarged lacrimal glands, biopsy of these sites is warranted. When no obvious or visible lesion is identified, Ga\textsuperscript{67} scan or chest CT scan should be done, aiming to pinpoint sites to biopsy. If the Ga\textsuperscript{67} scan is negative, transbronchial lung biopsy should be performed, irrespective of whether chest CT scan shows specific aberrations. If bronchoscopy is negative and chest CT scan demonstrates intrathoracic adenopathy, mediastinoscopy should be performed. If these maneuvers are negative, I do not recommend "blind" biopsies of conjunctiva, muscle, or liver, as the yields are too low. If an extracranial histologic diagnosis cannot be reached, an empiric trial of high dose corticosteroid therapy should be initiated, provided the clinical course is consistent with sarcoidosis and appropriate follow-up can be assured.

References

Sarcoidosis of the Anterior Visual Pathway: 24 New Cases

Larry P. Frohman, MD, Medhat Guirgis, MD, Roger E. Turbin, MD, and Leonard Bielory, MD

Objectives: To describe the clinical spectrum and a rational approach to the diagnosis of anterior visual pathway sarcoidosis.

Methods: Retrospective chart review of all patients examined in neuro-ophthalmic consultation by 1 author from 1989 to 1998 with a diagnosis of sarcoidosis.

Results: There were 24 patients (17 female, 7 male, mean age 40 years) with anterior visual pathway sarcoidosis, 17 (71%) of whom were not previously known to have sarcoidosis. Visual acuity ranged from 20/20 to NLP. Normal fundi were observed in 15%. Among the 85% who had fundus abnormalities, pallor was present in 55%, disc edemas in 26%, periphlebitis/sheathing in 14%, and optic disc granuloma in 10%. Ten patients (42%) had uveitis, active in only 3 (13%). An elevated angiotensin-converting enzyme (ACE) was present in 16 (76%) of 21 patients tested; evidence of sarcoidosis on chest radiograph was present in 13 (72%) of 18; gallium scanning was abnormal in 13 (93%) of 14; neuroimaging abnormalities of the optic nerves, chiasm, or tract were present in 16 (70%) of 23; lymphocytic pleocytosis or elevated cerebrospinal fluid protein was identified in 14 (88%) of 16 patients, with both values elevated in 7 (44%) patients. Histologic confirmation was obtained in 13 (81%) of 16 who underwent biopsy; in the remaining patients, diagnosis was based entirely on clinical and laboratory evidence.

Conclusions: Anterior visual pathway disease may be underrecognized as a presentation of sarcoidosis. Classic fundus findings of periphlebitis and optic granuloma are typically absent. An aggressive diagnostic evaluation may help establish the diagnosis early in its course.

(J Neuro-Ophthalmol 2003;23: 190-197)

Sarcoidosis is a multisystem disease that most frequently targets the respiratory system. Ocular involvement has been said to occur in 22% of cases (1). Neurologic involvement occurs in about 5-16% of cases (2). Involvement of the optic nerve, chiasm, and tract (anterior visual pathway, or AVP) in neurosarcoidosis is said to be uncommon, involving 1-5% of cases (3), although single case reports of sarcoid optic neuropathy are often published in major journals. However, we believe AVP sarcoidosis is frequently and erroneously labeled idiopathic optic neuropathy when supporting clinical signs go unrecognized and a directed diagnostic strategy is not used. When the AVP is involved in a patient with known sarcoidosis, the diagnosis is relatively straightforward. However, if AVP disease is seen in the absence of known sarcoidosis, it is imperative to establish the systemic diagnosis. In prior series, irreversible visual loss has often occurred as a result of delayed diagnosis or even iatrogenic trauma when biopsies were taken of the optic nerves or when they were resected for presumed meningioma or other suspected disease processes (3-6). Although optic nerve or nerve sheath biopsy may ultimately be indicated in selected cases to preserve the vision in the fellow eye, the astute clinician may often arrive at the diagnosis by more uniformly applying a tailored diagnostic strategy.

MATERIALS AND METHODS

We reviewed the database of all cases seen in neuro-ophthalmic consultation by 1 of us (LPF) from 1989 to 1998 and identified 69 patients with sarcoidosis. This study focused on the clinical features and diagnostic testing of the 24 cases with AVP disease from sarcoidosis whose records were recoverable. The results of the assessment of the non-AVP cases have been previously published in this Journal (7). Examination included Snellen visual acuity, color vision (typically using Ishihara plates), presence of a relative afferent pupillary defect (RAPD), ocular motility, assessment of the adnexa, visual field (usually automated testing of central 24° or 30°), stereo biomicroscopy, and indirect ophthalmoscopy.

Diagnostic studies included serum angiotensin-converting enzyme (ACE), purified tuberculin protein
Sarcoidosis of the AVP

The clinical features of the 24 cases of sarcoidosis of the AVP are shown in Table 1. Patients 1–17 did not have known sarcoidosis at the time of presentation. The mean age at the time of presentation to our service was 40 years (range 25–75 years). Seventeen patients (71%) were women. Six (25%) patients had unilateral and 18 (75%) had bilateral visual loss at presentation (total of 42 affected eyes). Despite bilateral disease, 16 (67%) had a RAPD detected at the initial examination.

The median visual acuity in the 42 involved eyes was between 20/30 and 20/40 (Fig 1). Four eyes (9.5%) had no light perception, four (9.5%) had counting fingers, hand motion, or light perception; five (12%) had 20/100–20/400; 12 (29%) had 20/30–20/70; and 17 involved eyes (40%) had 20/25 acuity or better. In the 21 involved eyes with acuity of 20/30 or better that underwent color vision testing, 9 (43%) had abnormalities.

The visual field defects seen in the 34 of 42 eyes tested are summarized in Table 2. Fundus findings are presented in Table 3.

Optic disc pallor was the most common sign, seen in 55% of involved eyes. Optic disc edema was seen in 29% of eyes. Periphlebitis or other vascular sheathing was seen in only 14% of involved eyes (Fig. 2). Optic disc granulomas were seen in 10% of involved eyes (Fig. 3). Less frequently seen funduscopic findings included disc hemorrhage, optic disc telangiectasia, macular exudate, optic disc shunt vessels, and vitreous "snowballs." No fundus abnormalities were detected in 12% of involved eyes. Phosphenes/phos­topsias were reported by 8%.

In addition to the involvement of the AVP, other ophthal­mic signs at presentation included diplopia (13%) and ocular pain (13%). Evidence of past or active anterior uveitis was present in 42%, including 1 patient with Busacca nodules. Among 70% of the patients with anterior uveitis, 7 (70%) did not have known sarcoidosis at the time of presentation. Of these 7, only 3 (43%) had evidence of active uveitis at the time of presentation; the others demonstrated old mutton-fat keratic precipitates. In the 3 cases of uveitis in patients with previously diagnosed sarcoidosis, 2 (67%) had active uveitis at presentation. Six patients (25%) had clinical evidence of lacrimal gland enlargement, 3 (13%) had proptosis, and 3 (13%) had ptosis.

Other neurologic deficits included hearing loss in 2 patients (8%), facial nerve palsy in 2 patients (8%), sixth cranial nerve palsy in 1 patient (4%), unilateral hypoaesthesia in the territory of all branches of the trigeminal nerve in 1 patient (4%), third cranial nerve palsy in 1 patient (4%), and hemiparesis in 1 patient (4%).

Three patients (13%) had diabetes insipidus, each had previously been diagnosed with sarcoidosis, and had visual field defects that corresponded to chiasmal or optic tract involvement.

Diagnostic Evaluation

Of 21 patients who had a serum ACE performed, 16 (76%) were abnormal. Chest radiography showed radiographic evidence of sarcoidosis in 13 (72%) of 18 patients who underwent this study. Of the 17 patients who underwent both chest radiograph and ACE testing, both were normal in 4 (24%). Of the 14 patients who underwent gallium scintigraphy either before or at time of visual presentation, 13 (93%) demonstrated abnormalities consistent with sarcoidosis. These included abnormal uptake in the glandular tissue (lacrimal, parotid, and submandibular glands) in 7 (50%) or lung parenchyma in 11 (79%). Because 58% of patients with positive gallium scans will either improve or normalize after 4–12 months of corticosteroid therapy (8), we excluded 1 negative gallium scan that was performed after 1 full year of corticosteroid treatment (Patient 13). Ten patients without known sarcoidosis who underwent gallium scanning at the time of acute visual loss demonstrated abnormalities consistent with sarcoidosis (Table 4).

Twelve (80%) of the 15 patients who underwent pul­monary function testing had abnormal results, and 4 (57%) of 7 patients tested were anergic. Twenty-four-hour urinary calcium excretion was abnormal in 4 (67%) of 6 patients tested.

Of 23 patients who underwent neuroimaging (20 MRI, 3 CT), 16 (70%) demonstrated involvement of the AVP (Figs. 4 and 5). Eight (35%) had bilateral optic nerve involvement, 6 (26%) had unilateral optic nerve involvement, 9 (39%) had involvement of the sella/chiasm/pituitary/suprasellar area, 2 (9%) had optic tract involvement, and 2 (9%) had an orbital component. Two of the 7 patients with normal neuroimaging only had CT scans; both had optic nerve head granulomas.

Of 16 patients who underwent lumbar puncture, 14 (88%) had either lymphocytic pleocytosis or elevated protein. Lymphocytic pleocytosis was identified in 11 (69%) and elevated cerebrospinal fluid (CSF) protein in 10 (63%). Both values were elevated in 7 (44%).
<table>
<thead>
<tr>
<th>Pt. no.</th>
<th>Age/sex</th>
<th>Known sarcoid at presentation</th>
<th>Initial visual acuity OD, OS</th>
<th>RAPD</th>
<th>Ishihara color plates OD, OS</th>
<th>Visual field OD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28/M</td>
<td>No</td>
<td>20/20, CF10</td>
<td>OS</td>
<td>10/10, 0/10</td>
<td>NL</td>
</tr>
<tr>
<td>2</td>
<td>35/F</td>
<td>No</td>
<td>HM, NLP</td>
<td>OS</td>
<td>Unable</td>
<td>Unable</td>
</tr>
<tr>
<td>3</td>
<td>28/F</td>
<td>No</td>
<td>CF 20/20</td>
<td>OD</td>
<td>0/10, 8/10</td>
<td>Unable</td>
</tr>
<tr>
<td>4</td>
<td>56/F</td>
<td>No</td>
<td>20/40, 20/30</td>
<td>OD</td>
<td>10/10, 8/10</td>
<td>PC</td>
</tr>
<tr>
<td>5</td>
<td>41/F</td>
<td>No</td>
<td>20/20, 20/30</td>
<td>OS</td>
<td>10/10, 10/10</td>
<td>DD</td>
</tr>
<tr>
<td>6</td>
<td>32/F</td>
<td>No</td>
<td>NLP, 20/20</td>
<td>OD</td>
<td>Unable 10/10</td>
<td>Unable</td>
</tr>
<tr>
<td>7</td>
<td>33/M</td>
<td>No</td>
<td>20/100, 29/25</td>
<td>OD</td>
<td>1/10, 10/10</td>
<td>DD, CC</td>
</tr>
<tr>
<td>8</td>
<td>41/F</td>
<td>No</td>
<td>20/30, 20/30</td>
<td>OS</td>
<td>6/6, 6/6</td>
<td>NL</td>
</tr>
<tr>
<td>9</td>
<td>62/M</td>
<td>No</td>
<td>20/20, 20/60</td>
<td>OS</td>
<td>14.5/15, 9.5/15</td>
<td>NL</td>
</tr>
<tr>
<td>10</td>
<td>75/F</td>
<td>No</td>
<td>20/30, 20/20</td>
<td>OD</td>
<td>6/10, 9.5/10</td>
<td>NL</td>
</tr>
<tr>
<td>11</td>
<td>50/F</td>
<td>No</td>
<td>20/25, NLP</td>
<td>OS</td>
<td>10/10, Unable</td>
<td>AL</td>
</tr>
<tr>
<td>12</td>
<td>30/F</td>
<td>No</td>
<td>20/20, 20/20</td>
<td>No</td>
<td>10/10, 10/10</td>
<td>SD</td>
</tr>
<tr>
<td>13</td>
<td>38/M</td>
<td>No</td>
<td>20/20, 20/25</td>
<td>Not done</td>
<td>Not done</td>
<td>BS</td>
</tr>
<tr>
<td>14</td>
<td>32/F</td>
<td>No</td>
<td>20/20, 20/70</td>
<td>OS</td>
<td>10/10, 9/10</td>
<td>NL</td>
</tr>
<tr>
<td>15</td>
<td>36/F</td>
<td>No</td>
<td>20/20, 20/20</td>
<td>No</td>
<td>10/10, 10/10</td>
<td>NL</td>
</tr>
<tr>
<td>16</td>
<td>29/F</td>
<td>No</td>
<td>20/30, 20/25</td>
<td>No</td>
<td>6.5/10, 7/10</td>
<td>AL, NS</td>
</tr>
<tr>
<td>17</td>
<td>50/F</td>
<td>No</td>
<td>20/20, 20/20</td>
<td>No</td>
<td>4,5/6, 6/6</td>
<td>SD, NS</td>
</tr>
<tr>
<td>18</td>
<td>33/M</td>
<td>Yes</td>
<td>20/25, 20/30</td>
<td>OD</td>
<td>8.5/10, 2.5/10</td>
<td>Left HH</td>
</tr>
<tr>
<td>19</td>
<td>54/F</td>
<td>Yes</td>
<td>20/200, 20/200</td>
<td>No</td>
<td>6/10, 6/10</td>
<td>Unable</td>
</tr>
<tr>
<td>20</td>
<td>25/M</td>
<td>Yes</td>
<td>20/40, 20/200</td>
<td>No</td>
<td>5.5/10, 6/10</td>
<td>BT</td>
</tr>
<tr>
<td>21</td>
<td>41/F</td>
<td>Yes</td>
<td>20/30, LP</td>
<td>OD</td>
<td>12/12, Unable</td>
<td>Right hemifield defect</td>
</tr>
<tr>
<td>22</td>
<td>39/F</td>
<td>Yes</td>
<td>20/25, 20/40</td>
<td>OS</td>
<td>9/10, 8.5/10</td>
<td>DD</td>
</tr>
<tr>
<td>23</td>
<td>25/F</td>
<td>Yes</td>
<td>20/25, 20/25</td>
<td>No</td>
<td>8/10, 8/10</td>
<td>BT</td>
</tr>
<tr>
<td>24</td>
<td>46/M</td>
<td>Yes</td>
<td>20/400, NLP</td>
<td>OS</td>
<td>Unable</td>
<td>Unable</td>
</tr>
</tbody>
</table>

Sixteen patients (Table 5) underwent a total of 19 biopsies (including a mediastinoscopy in Patient 2 that was abandoned due to hemorrhage before tissue was obtained). Overall, 13 patients (81%) had histopathology consistent with sarcoidosis (noncaseating granulomas). All biopsies were positive in the seven patients with a previous clinical diagnosis of sarcoidosis who developed AVP involvement. Six (67%) of 9 patients without known sarcoidosis who permitted biopsy had histologic confirmation and the other 3 with negative biopsies had overwhelming clinical evidence supporting the diagnosis of sarcoidosis. For example, Patient 2 had an abnormal ACE, chest radiograph, gallium scan, pulmonary function testing, 24-hour urine calcium excretion, and MRI scan; Patient 16 had an abnormal chest radiograph, gallium scan, anergy panel, MRI scan, and lumbar puncture, as well as lacrimal gland enlargement; Patient 17 had an abnormal ACE, chest radiograph, gallium scan, pulmonary function testing, 24-hour urine calcium, and lumbar puncture. All eight patients (Patients 3, 6, 7, 10, 11, 12, 14, and 15) who refused biopsy had overwhelming clinical and laboratory or radiologic evidence to support the diagnosis of sarcoidosis (Tables 1, 4, and 5).
### TABLE 1. Continued

<table>
<thead>
<tr>
<th>Visual field</th>
<th>Other manifestations</th>
<th>Fundus OD</th>
<th>Fundus OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>DD, AL</td>
<td>Inactive uveitis, lacrimal gland enlargement</td>
<td>Disc edema with hemorrhages, telangiectasia, periphlebitis</td>
<td>NL</td>
</tr>
<tr>
<td>NS</td>
<td>Third nerve palsy OD, proptosis</td>
<td>Disc edema with hemorrhages, telangiectasia, periphlebitis</td>
<td>NL</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Involvement of the AVP in sarcoidosis may be secondary to extrinsic granuloma compressing the nerve, intrinsic infiltration with or without visible optic nerve granuloma, compression or infiltration of the chiasm, or raised intracranial pressure without ventriculomegaly. Elevated intracranial pressure without ventriculomegaly may occur if meningeal inflammation interferes with cerebrospinal fluid egress (9). AVP sarcoidosis may be encountered in the face of known pulmonary sarcoidosis or its other protean systemic manifestations. It may, however, be the presenting sign of the disease (10). Lower found that 71 (13%) of 554 patients with sarcoidosis at a single institution had neurologic manifestations. Although facial nerve palsy was the most common neurologic manifestation (7%), optic neuropathy was seen in 7 cases (1%). In the series of 520 cases...

---

AL, arcuate loss; BS, enlarged blind spot; BT, bitemporal hemianopsia; CC, cecocentral scotoma; CF, count fingers; DD, diffuse depression; HH, homonymous hemianopsia; HM, hand motion; NL, normal; NLP, no light perception; NS, nasal step; PC, paracentral scotoma; RAPD, relative afferent pupil defect; SD, superior depression.

---

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

TABLE 2. Visual field defects in 34 eyes

<table>
<thead>
<tr>
<th>Field defect</th>
<th>Number of eyes</th>
<th>Percent of visual fields performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporal, bitemporal, or homonymous hemianopia</td>
<td>9</td>
<td>26</td>
</tr>
<tr>
<td>Arcuate/nasal step</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>Diffuse depression</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Superior depression</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Blind spot enlargement</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Paracentral scotoma</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Cecocentral scotoma</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Normal</td>
<td>5</td>
<td>15</td>
</tr>
</tbody>
</table>

TABLE 3. Fundus manifestations in 42 eyes

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Number of eyes</th>
<th>Percent of involved eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disc pallor</td>
<td>23</td>
<td>55</td>
</tr>
<tr>
<td>Disc edema</td>
<td>11</td>
<td>26</td>
</tr>
<tr>
<td>Periphlebitis/sheathing</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>Disc granuloma</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Disc hemorrhage</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Retinal telangiectasia</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Macular exudate</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Disc shunt vessel</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Vitreous &quot;snowball&quot;</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Normal</td>
<td>5</td>
<td>12</td>
</tr>
</tbody>
</table>

FIGURE 2. Right fundus shows multiple shunt vessels on disc and obvious periphlebitis of most veins, most noticeable in superotemporal branch vein (Patient 6).

of sarcoidosis reported by Recio et al. (11), 42 (8%) had neurologic disease; only 7 (1%) had visual loss. In that series, 59% of cases with neurologic disease did not present with any other systemic manifestations of sarcoidosis.

FIGURE 3. Left fundus shows large optic disc granuloma (Patient 14).
Many cases of occult sarcoidosis presenting with isolated optic neuropathy have reportedly required optic nerve biopsy to establish the diagnosis, obviating any chance of visual recovery (12–14). In other cases, diagnosis was established only at autopsy. In a series of 4 cases of AVP sarcoidosis, Beck et al. (15) reported only 1 case that had systemic involvement at the time of the presentation; 2 of the remaining 3 required optic nerve biopsy to establish the diagnosis. Ng et al. (4) described chiasmal involvement as the initial manifestation of sarcoidosis in a 14-year-old girl. Although MRI showed leptomeningeal enhancement, an optic nerve biopsy was used to demonstrate sarcoidosis. Pelton et al. (16) described a patient with increased intracranial pressure without ventriculomegaly who required optic nerve histopathology to disclose sarcoidosis as the cause.

In a 1997 review of 18 cases of biopsy-proven sarcoid optic neuropathy compiled from the English literature, Ing et al. (3) found that sarcoidosis was often confused with optic nerve meningioma in patients who demonstrated no other systemic signs, necessitating biopsy to establish the diagnosis.

Our review suggests that when patients with undiagnosed sarcoidosis first present with visual loss, other systemic signs may act as clues to a diagnosis. In many cases, a careful history and ophthalmic examination and subsequent directed laboratory/radiologic investigation will allow diagnosis of “occult” sarcoidosis without resorting to optic nerve biopsy.

The diagnostic strategy typically begins with an ACE level and a chest radiograph. Serum levels of ACE are said to be elevated in 70–80% of patients with “active disease” (17) referring to active pulmonary disease. The current series finds that ACE was elevated in 76% of cases of sarcoidosis of the AVP. This contrasts with our earlier finding that ACE was elevated in only 27% of cases with neuro-ophthalmic sarcoidosis other than AVP involvement (7).

In this series, 72% of cases had an abnormal chest radiograph. This is similar to our experience with other forms of neuro-ophthalmic sarcoidosis (7). Three of the five patients who had a normal chest radiograph also had a normal ACE. The 2 patients without an antecedent diagnosis of sarcoidosis had systemic involvement at the time of presentation.

### Table 4. Diagnostic Evaluation

<table>
<thead>
<tr>
<th>Pt. no.</th>
<th>ACE</th>
<th>CXR</th>
<th>Gallium scan</th>
<th>PFT</th>
<th>Anergy</th>
<th>Urine Ca</th>
<th>Brain imaging</th>
<th>LP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>NP</td>
<td>NP</td>
<td>A</td>
<td>NP</td>
</tr>
<tr>
<td>2</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>NP</td>
<td>A</td>
<td>A</td>
<td>N</td>
</tr>
<tr>
<td>3</td>
<td>A</td>
<td>NP</td>
<td>A</td>
<td>A</td>
<td>NP</td>
<td>NP</td>
<td>A</td>
<td>NP</td>
</tr>
<tr>
<td>4</td>
<td>N</td>
<td>N</td>
<td>A</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>5</td>
<td>A</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>N</td>
<td>NP</td>
</tr>
<tr>
<td>6</td>
<td>N</td>
<td>N</td>
<td>A</td>
<td>A</td>
<td>NP</td>
<td>N</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>7</td>
<td>N</td>
<td>A</td>
<td>NP</td>
<td>NP</td>
<td>A</td>
<td>NP</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>8</td>
<td>A</td>
<td>N</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>9</td>
<td>A</td>
<td>NP</td>
<td>NP</td>
<td>A</td>
<td>NP</td>
<td>A</td>
<td>NP</td>
<td>NP</td>
</tr>
<tr>
<td>10</td>
<td>A</td>
<td>N</td>
<td>A</td>
<td>N</td>
<td>NP</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>11</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>12</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>NP</td>
<td>N</td>
<td>N</td>
<td>A</td>
</tr>
<tr>
<td>13</td>
<td>A</td>
<td>A</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
</tr>
<tr>
<td>14</td>
<td>A</td>
<td>A</td>
<td>NP</td>
<td>NP</td>
<td>N</td>
<td>NP</td>
<td>N</td>
<td>NP</td>
</tr>
<tr>
<td>15</td>
<td>NP</td>
<td>NP</td>
<td>A</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>N</td>
<td>NP</td>
</tr>
<tr>
<td>16</td>
<td>N</td>
<td>A</td>
<td>A</td>
<td>N</td>
<td>A</td>
<td>NP</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>17</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>N</td>
<td>A</td>
<td>N</td>
<td>A</td>
</tr>
<tr>
<td>18</td>
<td>NP</td>
<td>A</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>19</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>N</td>
<td>NP</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>20</td>
<td>A</td>
<td>A</td>
<td>NP</td>
<td>N</td>
<td>NP</td>
<td>NP</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>21</td>
<td>A</td>
<td>A</td>
<td>NP</td>
<td>A</td>
<td>NP</td>
<td>NP</td>
<td>A</td>
<td>NP</td>
</tr>
<tr>
<td>22</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>NP</td>
<td>N</td>
<td>N</td>
<td>A</td>
</tr>
<tr>
<td>23</td>
<td>A</td>
<td>NP</td>
<td>A</td>
<td>A</td>
<td>NP</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>24</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>A</td>
<td>NP</td>
<td>NP</td>
<td>A</td>
<td>A</td>
</tr>
</tbody>
</table>

| % ABNL | 76  | 72  | 93  | 80  | 57  | 67  | 70  | 88  |

A, abnormal; ACE, angiotensin-converting enzyme; CXR, chest radiograph; LP, lumbar puncture; N, normal, NP, not performed; PFT, pulmonary function testing; Urine Ca, 24-hour urine calcium excretion.
sarcoidosis who had both a negative chest radiograph and a negative ACE were detected by gallium scan. In our series, this was the most effective screening test, being abnormal in 93% of cases. Unlike Kosmorsky et al. (18), we do not routinely use CT of the chest. Our preference for the gallium scan is based on its ability to identify potential sites of active disease in the chest and elsewhere from which one can obtain histologic diagnosis.

High-resolution MRI of the brain, including contrast and fat-suppressed views of the optic nerves, is the neuro-radiologic procedure of choice in evaluation of sarcoidosis of the AVP. In previous reports, the most common imaging finding has been diffuse enlargement of the optic nerve, as well as thickening and enhancement of the optic nerve dura ("tram-tracking") (3). Ng et al. (4) have suggested that sarcoidosis may radiologically resemble the peripheral leptomeningeal enhancement of an optic nerve or chiasmal glioma. Mafee has suggested that abnormal dural enhancement of the optic nerve or enlargement of the intracranial segment of the optic nerve is suggestive of sarcoidosis (19).

We have previously reported that we suspect sarcoidosis if the optic nerve enhances from globe to chiasm (20) (Fig. 4) or if there is noncontiguous involvement of the contralateral nerve, especially if the involvement is "nodular" (Fig. 5). Such "stem-to-stern" involvement of the optic nerve, particularly in the presence of enhancement of the frontal-basilar meninges, is very suggestive of sarcoidosis. In our experience, the latter finding may be overlooked, and is best seen in the coronal images anterior to the sella turcica. Enhancement of other cranial nerves may be seen. An enlarged and enhancing lacrimal gland in conjunction with such optic nerve involvement is also a sign that mandates a careful evaluation for occult sarcoidosis. Contrast MRI findings less specific for sarcoidosis include periventricular white matter lesions and intraaxial or extraaxial masses (21).

The characteristic spinal fluid findings described in neurosarcoidosis are lymphocytic pleocytosis and elevated cerebrospinal fluid protein (6). In our series, 88% of cases had 1 of these findings, and 44% had both, but they are nonspecific. We have stopped obtaining cerebrospinal fluid ACE levels because of low sensitivity, even in cases with known histologic confirmation of sarcoidosis.

### TABLE 5. Biopsy results in 9 cases without preexisting diagnosis*

<table>
<thead>
<tr>
<th>Site of biopsy</th>
<th>No. of biopsies</th>
<th>No. positive</th>
<th>% Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orbit</td>
<td>1</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Bronchoscopy</td>
<td>2</td>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>Mediastinoscopy</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lacrimal gland</td>
<td>3</td>
<td>1</td>
<td>33</td>
</tr>
<tr>
<td>Nasal mucosa</td>
<td>1</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Pantracheal node</td>
<td>1</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Skin</td>
<td>2</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
<td>12*</td>
<td>6</td>
<td>50</td>
</tr>
</tbody>
</table>

* Three cases each underwent two biopsies.
† Includes 1 case where biopsy was aborted due to excessive bleeding.
Sarcoidosis of the AVP

We generally perform pulmonary function testing, energy panels (with a PPD), and 24-hour urine calcium excretion. These noninvasive tests were abnormal in 80%, 57%, and 67%, respectively, of our patients tested. Although offering supportive evidence, they are not specific tests.

We encourage histologic confirmation of the diagnosis of sarcoidosis, given the toxicity of corticosteroid and more aggressive immunomodulatory treatment. If there is no obvious superficial lesion to biopsy (conjunctival or cutaneous nodule, enlarged lacrimal gland), we use the gallium scan as a guide to a deeper biopsy site, trying the most accessible "hot spot" first. Using this approach in patients without a prior diagnosis of sarcoidosis, we took biopsy specimens of pulmonary tissue 4 times, the lacrimal gland 3 times, a cutaneous nodule twice, and a paratracheal node, the orbit, and nasal tissue once each. If no clinically visible lesion is present, and nothing is demonstrated by gallium scan (or chest CT if that technique is used), options include biopsy of the liver, especially if abnormalities in liver function testing are present, multiple conjunctival biopsies, or bronchoscopy. In some cases, rather than performing an "undirected biopsy," if multiple laboratory/radiologic evaluations indicate likely sarcoidosis, we may treat without histologic confirmation.

In the work-up of suspected AVP sarcoidosis, we recommend obtaining, in addition to the MRI, ACE, and chest radiograph, a 24-hour urine collection, PPD and energy panel, pulmonary function tests, a lumbar puncture, and a gallium scan. It is preferable to obtain these tests before therapy with corticosteroid agents is begun, as this medication may rapidly "normalize" these tests. Even with such a diagnostic strategy, there may be cases where obtaining an optic nerve biopsy is the only way to be sure of the diagnosis (21).

REFERENCES

Latent Nystagmus and Acquired Pendular Nystagmus Masquerading as Spasmus Nutans

Jaeil I. Kim, MD, PhD, Louis F. Dell'Osso, PhD, and Elias Traboulsi, MD

Abstract: We used ocular motility recordings to identify the characteristics of a rare combination of conjugate, horizontal jerk, and pendular nystagmus in a 9-year-old boy. The clinical diagnoses were amblyopia, left esotropia, congenital nystagmus, and an apparently unioocular pendular nystagmus that mimicked spasmus nutans. Ocular motility recordings revealed an unusual latent/manifest latent nystagmus, pendular nystagmus with characteristics of an acquired nystagmus, and unioocular saccades. The ocular motor data identified clinically unrecognized types of nystagmus and suggested that the pendular nystagmus was acquired in infancy rather than as a result of failure to develop good vision or binocularity. The presence of unioocular saccades adds to the mounting evidence that individual control for each eye exists in humans. (J Neuro-Ophthalmol 2003;23: 198-203)

Complex ocular motor cases often present the clinician with a diagnostic puzzle whose multiple, sometimes-contradictory signs require ocular motility recordings to solidify diagnosis. Analysis of the data from such cases may also provide insight into the organization of the ocular motor system.

In this study, we describe a patient with a rare combination of latent/manifest latent nystagmus (LMLN) and a reversed Alexander law variation, together with apparently unioocular pendular nystagmus and unioocular saccades. In doing so, we address the following questions: 1) Is the nystagmus the result of failure to develop normal binocular vision? 2) Is the nystagmus worse in the amblyopic eye? 3) Is a visual acuity better than 20/100 required to prevent the development of pendular nystagmus and to preserve the strong yoking needed to ensure conjugate eye movements? We also present data-driven diagnoses, therapeutic recommendations, and support for the hypothesis of unioocular motor control (1).

We use the term LMLN to include both latent nystagmus (nystagmus evoked by having one eye occluded) and manifest latent nystagmus (nystagmus present with both eyes open, one fixating and the other suppressed) (2). Regardless of viewing condition, the linear or decelerating slow phases of both eyes are in the nasal direction of the fixating eye and the fast phases in the temporal direction (2,3). We use the term congenital nystagmus (CN) to mean a conjugate nystagmus with characteristic pendular or jerk waveforms that are not normally related to strabismus or to the fixating eye (4). CN may have a superimposed "latent component" but the waveforms remain those of CN.

CASE REPORT

Clinical Features

The patient, a boy, was the product of a 32-week gestation with a small subarachnoid hemorrhage noted by lumbar puncture performed in the nursery. A neurologic evaluation at the age of 4 months disclosed intermittent left fisting and mild head lag. At 12 months, he showed slight delay in cognitive and motor skills. He had developed an alternating esophoria at 18 months, and exhibited minor developmental and motor delay. Apart from intermittent left fisting, his neurologic examination was normal. At 30 months, dissociated pendular nystagmus (left eye greater than right eye) was diagnosed as spasmus nutans; jerk nystagmus was diagnosed as congenital. An intermittent left head tilt was noted at age 2 years.

On our initial examination at age 9 years, visual acuity was 20/30 right eye and 20/100 left eye. An esotropia of 25 prism-diopters was noted. There was a conjugate, horizontal jerk-right nystagmus with a left face turn and a constant, apparently unioocular, horizontal pendular nystagmus in the left eye that was clinically compatible with spas-
Pseudo Spasmus Nutans

He had bilateral dissociated vertical deviations (DVD) more prominent in the right eye. There was significant bilateral overaction of the inferior oblique muscles. A left face turn was present when he fixated on a distant target. Using the Titmus test, we confirmed that there was no stereopsis. He reported no oscillopsia.

Testing Methods

Horizontal eye movement recordings were made using infrared reflection (Applied Scientific Laboratories, Waltham, MA). In the horizontal plane, the system was linear to ±20° and monotonic (i.e., no reversal) to ±25–30° with a saturating characteristic. The sensitivity was 0.25°. The infrared signal from each eye was calibrated with the other eye behind cover to obtain accurate position information and to document small tropias and phorias hidden by the nystagmus. Eye positions and velocities (obtained by analog differentiation of the position channels) were displayed on a strip chart recording system (Beckman Type R612 Dynograph). The total system bandwidth (position and velocity) was 0-100 Hz. The data were digitized at 500 Hz with 16-bit resolution.

Written consent was obtained from the patient's parent before the testing. All test procedures were carefully explained to the patient before the experiment began and were reinforced with verbal commands during the trials. The patient was seated in a chair with headrest and a chin stabilizer, 5 feet from an arc of red light-emitting diodes (LEDs) to prevent convergence effects. At this distance, the LED subtended less than 0.1° of visual angle. The room light could be adjusted from dim down to blackout to minimize extraneous visual stimuli. Trials were kept short to guard against boredom because CN intensity is known to decrease with inattention.

Data Analysis

Data analysis (and filtering, if required) and graphical presentation were performed using MATLAB (The Math-Works, Natick, MA) software for scientific computing.

RESULTS

Nystagmus Waveforms and Directions

Ocular motility recordings did not contain the typical CN waveforms previously identified (4). Figure 1 shows the waveforms during fixation in primary position of the right (Fig. 1A) and left eye (Fig. 1B) during LN (one eye occluded) and of the right eye (Fig. 1C) during MLN (both eyes viewing). The waveforms were jerk and dual jerk with linear or decelerating slow phases; these are the waveforms of LMLN. When recorded during monocular fixation (one eye occluded), the direction of the jerk nystagmus was always towards the fixating eye and, during binocular viewing, the direction was also always towards the fixating eye, with the other eye in an esotropic position (25 PD). As this and the following figures show, the fast phases of the LMLN in the two eyes were often dissociated.

FIG. 1. Infrared eye movement recording. There is horizontal, dual jerk nystagmus of both eyes in primary position with right eye fixation (A) and left eye fixation (B) during monocular viewing, and with right eye fixation (C) during binocular viewing. In each case, the jerk nystagmus is in the direction of the fixating eye, a characteristic of latent/manifest latent nystagmus (LMLN). REH, right eye horizontal; LEH, left eye horizontal; us, unisaccadic; rightward eye movements are positive. Figures 1 and 3–6 show intervals from 30-second records. BE = both eyes.

Nystagmus Variation With Gaze Angle

Figure 2 shows the variation of the LMLN as the fixating right eye is directed laterally to the right (Fig. 2A) and left (Fig. 2B). The LMLN slow-phase velocity and amplitude decreased (while the esotropia remained constant) as gaze was directed to the right while the right eye was fixating the targets. Even in far-left gaze, when the esotropia of the left eye diminished (damping the LMLN amplitude), the right eye remained the fixating eye and the LMLN direction remained jerk right.

Interocular Phase of Pendular Nystagmus

Recordings documented that the pendular nystagmus that appeared clinically as 'unisaccadic' was, in fact, present in both eyes but greater in the left eye. As Figure 1 shows, changing the fixating eye did not alter the 8-Hz pendular component of the nystagmus; it remained 6–10 times greater in the left eye. Expanded time scale intervals of the pendular nystagmus in both eyes revealed interocular phase differences of either 45° or 135°. Figure 3 shows an interval of 2 LMLN cycles (15 pendular cycles) in which the in-
A. BE Viewing RE Fixation

B. BE Viewing RE Fixation

FIG. 2. Infrared eye movement recording. This shows variation of the nystagmus with gaze to the right (A) and left (B) with right eye fixation during binocular viewing and the left eye in an esotropic position, except for far left gaze angles. The increase in nystagmus as the fixating eye abducts is a reversal of the Alexander law variation usually seen in LMLN.

The interocular phase shift of the pendular nystagmus was 45° (the fixating right eye was leading the left).

Saccade and Fast-Phase Damping of Pendular Nystagmus

Prominent throughout the recordings were periods of transient damping of the pendular nystagmus immediately after voluntary saccades and, in some cases, after nystagmus fast phases. Figure 4 demonstrates the transient damping of the pendular nystagmus after voluntary saccades (A) and some fast phases (B). Voluntary saccades in the direction of jerk nystagmus fast phases (s1, s3, and s4) and opposite to them (s2) damped the pendular nystagmus transiently. The damping is more easily seen in the variation of the velocity trace.

Dissociated and Unocular Saccades

The patient exhibited dissociated (unequal amplitude), convergent, divergent, and occasional unocular saccades in addition to normal, conjugate saccades (i.e., saccades with normal peak velocity- and duration-amplitude relationships). Square-wave jerks were common; some were disconjugate or unocular. The unocular saccades and square-wave jerks appeared in the fixating right eye during fixation of a stationary LED target; none were seen in the deviated left eye. The rightward saccade at 19 seconds in Figure 1A was greater in the right eye but the leftward saccade at 19.3 seconds was greater in the left eye. The rightward saccade that followed at 19.8 seconds was so dissociated (much greater in the left eye) that it was almost unocular. Figure 5 shows the eye position, velocity, acceleration, and jerk (the third derivative of position) of both eyes during divergent, convergent, and dissociated saccades. Figure 6 shows the same data for a truly unocular
FIG. 5. Infrared eye movement recording. Eye position, velocity, acceleration, and jerk recordings from both eyes show that a divergent (dv) saccade is followed by convergent (cv) and dissociated (ds) saccades. The rapid deflections in the velocity, acceleration, and jerk data of both eyes confirm these simultaneous, albeit disjunctive, saccades. In this and Figure 6, the nonfixating left eye velocity, acceleration, and jerk data have been offset upwards for clarity.

leftward saccade (us), recorded from the fixating right eye, that exhibited saccadic duration, peak velocity, acceleration, and jerk. The uniocular saccade was followed by a conjugate saccade. As the top two panels in Figure 6 show, this 4° saccade had a peak velocity of 150°/s, which is normal for our laboratory. The patient’s conjugate saccades also met normal criteria, regardless of when in the cycle of the pendular nystagmus they occurred. Uniocular square-wave jerks also were recorded.

DISCUSSION

It is sometimes difficult to differentiate the subtle slow-phase characteristics of LMLN, CN, and combinations of the two (3). In this case, the positive alternate-cover test would have suggested LMLN, but only eye movement recordings could differentiate LMLN from CN with a latent component, the latter is much more common than LMLN.

Ocular motility recordings of the patient’s nystagmus demonstrated that it was actually LMLN with linear and decreasing velocity slow phases, despite a clinical picture of CN with a head turn and spasmus nutans (6). Monocular occlusion resulted in the direction of the jerk nystagmus switching to that of the fixating eye. There were no characteristic CN waveforms, although the presence of a conjugate, high-frequency pendular nystagmus superimposed on the jerk is common in both CN and LMLN.

The fixating eye in LMLN usually obeys Alexander law (3) and, in a similar manner, the amplitude of jerk CN increases as gaze is deviated away from the null angle. That is, jerk-right CN increases with rightward gaze and jerk-left CN increases with leftward gaze. Because of this, patients with LMLN commonly adopt a head turn or, if they alternate their fixating eye, two head turns. The head turn places the fixating eye in adduction, where the slow-phase velocity and the nystagmus are minimal. However, recordings of this patient’s LMLN variation with gaze angle (Fig. 2) revealed damping with abstraction of the fixating right eye, opposite to that predicted by Alexander law. That is, it was a reversed Alexander law variation. It was this phenomenon that accounted for the left head turn—not a CN null angle. A reversed Alexander law has been reported in some cases of LMLN (3).

The DVD in this patient was greater in the right eye, which was the preferred eye for fixation. Because only one eye is used for fixation in LMLN, the DVD has no effect on visual acuity. There is no diplopia because vision in the deviated eye is suppressed. The damped LMLN in right gaze was preferred for the increased acuity it allowed.

This patient’s pendular nystagmus differed from that in the dual jerk waveforms of either CN or LMLN (7). First, it was dissociated (much greater in the left eye than in the right) and did not change with fixation; in CN and LMLN, the pendular nystagmus is conjugate. Second, it was transiently damped by voluntary saccades and fast phases, a feature that does not occur in CN or LMLN. The pendular
nystagmus of spasmus nutans usually has a variable phase shift between the two eyes but is unaffected by saccades; this patient's interocular phase shift was either 45° or 135°. The eye movement data identified this as a nystagmus with the same characteristics as an acquired pendular nystagmus, consistent with other patients with acquired pendular nystagmus that we have recorded. We believe it improbable that this was the first recorded case of dual-jerk LMLN whose pendular component was damped by saccades. Also, the high frequency precluded oculopalatal myoclonus.

Based on our ocular motor diagnoses, we recommended an Anderson-Kestenbaum procedure to rotate both eyes to the left with an additional leftward rotation of the left eye. This would shift the low-nystagmus region towards primary position and correct the esotropia.

It is unique to have recorded dissociated, divergent, convergent, and uniocular saccades in a patient whose other ocular motor behavior is also unusual. It appears that the normally strong yoking seen in humans, even those with strabismus, has been weakened sufficiently in this patient to reveal an innate ability in humans to make uniocular saccades, that is, to fire only the burst cells to the agonist extraocular muscle of one eye. Because these saccades appeared in a subject with strabismus during fixation of an LED with no vergence stimuli, it is unlikely that they were due to superimposed vergence signals.

Uniocular saccades can be made by canines and humans (both are binocular mammals) (8–10). Thus, the current putative neuroanatomy whereby a single pool of burst neurons drives both eyes for ipsilateral saccades is, at best, inadequate and possibly incorrect. For that schema, one might speculate that the signal to the contralateral medial rectus could be blocked by inhibition at the level of the ipsilateral internuclear neurons in the region of the ipsilateral abducens motoneurons. That schema would allow an ipsilateral, uniocular, abducting saccade. However, the uniocular saccade shown in Figure 6 is an adducting saccade. Therefore, the ipsilateral internuclear neurons must have fired, innervating the contralateral oculomotor neurons via the MLF, with concurrent inhibition of the ipsilateral abducens motoneurons. Another possibility is that the uniocular saccades resulted from vergence burst neurons. These neurons fire during combined version–vergence refixations. However, it is unclear why vergence burst neurons specific to the fixating right eye's medial rectus would fire during fixation of a stationary LED target. The most parsimonious hypothesis is that each pool of burst neurons is made up of two subgroups, one specific for the ipsilateral abducens, the other for the contralateral oculomotor neurons (1). Recent evidence from the study of burst cells in monkeys supports the latter hypothesis (11–15). In cases of binocularity, a yoking mechanism coordinates the firing of both subgroups of burst cells so that conjugate saccades result. However, when binocularity is compromised, as in strabismus or achiasma, the yoking mechanism is weakened, allowing dissociated or uniocular saccades, consistent with an underlying uniocular architecture.

In our patient, the apparent uniocular pendular nystagmus exhibited the characteristics of an acquired, dissociated pendular nystagmus, perhaps caused by the subarachnoid hemorrhage in the neonatal period. Acquired pendular nystagmus is one of the more common types of nystagmus (16–18). Its pathogenesis remains unclear, and more than one mechanism may be responsible for its occurrence (19). High-frequency pendular nystagmus is known to accompany LMLN and CN, and may be associated with poor vision. Tusa et al. (20–22) studied the pendular nystagmus induced in monkeys reared using several occlusion paradigms. These authors concluded that this high-frequency pendular nystagmus was similar to that seen in CN and LMLN in humans. Their studies localized this nystagmus to the nucleus of the optic tract (NOT). Therefore, the pendular nystagmus sometimes seen superimposed on classic CN and LMLN waveforms (dual jerk and dual jerk latent waveforms) is possibly due to instability in NOT circuitry. The relationship between acuity and the development of binocular pendular nystagmus in more common cases of LMLN, DVD, strabismus, and amblyopia has not been adequately studied. Thus, there is a possibility that this patient's pendular nystagmus is a disconjugate variant of the NOT-produced pendular nystagmus.

Acknowledgments
We are grateful to Dr. Brian Moloney for allowing us the opportunity to study this unusual patient.

REFERENCES
Visual Outcome in Eyes With Asymptomatic Optic Disc Edema

Yehoshua Almog, MD, and Michaella Goldstein, MD

Background: Asymptomatic optic disc edema may last for months before conversion to anterior ischemic optic neuropathy (AION). Alternatively, the optic disc edema may resolve with preservation of normal vision. The conversion rate of asymptomatic optic disc edema to AION has not been prospectively studied. We prospectively followed patients with asymptomatic disc edema to determine this conversion rate.

Methods: The cohort was followed from 1991 to 2000 at a single ophthalmology clinic in Israel. There were 23 patients aged 47-74 years with asymptomatic disc edema and no signs of optic nerve dysfunction in whom the disc edema had been incidentally discovered on routine fundus examination performed for diabetes, hypertension, or follow-up after AION in the fellow eye.

Results: In 9 (36%) eyes, optic disc edema progressed to overt AION with a mean latency of 16.8 weeks (range 2-80 weeks). In 16 (64%) eyes, optic disc edema resolved without loss of vision with a mean latency of 15.5 weeks (range 4-44 weeks). The conversion rate to AION was 40% in patients who had had AION in the fellow eye, 31% in patients with diabetes, 43% in patients with diabetic retinopathy, and 0% in four amiodarone-treated patients.

Conclusion: Asymptomatic disc edema generally resolves with no visual loss, but one third of patients progress to full-blown AION. Diabetes mellitus is common in patients with asymptomatic optic disc edema. Perhaps patients diagnosed as having diabetic papillopathy actually have an impending AION that does not progress to overt disease.

(Patients with anterior ischemic optic neuropathy (AION) always manifest optic disc edema when presenting to the ophthalmologist with visual loss. In 1981, Hayreh (1), first described 4 visually asymptomatic patients in whom disc edema was diagnosed on a routine examination. Some of these patients, who had normal visual function, later developed typical symptomatic AION. Other patients have asymptomatic optic disc edema that resolves spontaneously. This phenomenon has been described mainly in diabetes mellitus (2) and has therefore been called "diabetic papillopathy." There is much confusion as to whether diabetic papillopathy and AION are the same entities. In 1997, Gordon et al (3) described 2 patients who had AION in 1 eye and asymptomatic optic disc edema in the fellow eye that resolved spontaneously. Spontaneous resolution of asymptomatic optic disc edema has also been described in patients treated with amiodarone (4,5).

The conversion rate of asymptomatic optic disc edema to symptomatic AION has never been prospectively studied. It was the purpose of this study to determine this rate and to characterize the patients who undergo conversion.

METHODS

Included in the study are 23 patients who attended the neuro-ophthalmology unit in the Tel-Aviv Medical Center from November 1991 through December 2000 with the diagnosis of asymptomatic optic disc edema. Most patients were referred for disc edema as incidentally discovered on routine fundus examination performed for diabetes or hypertension. In most others, the asymptomatic disc edema was incidentally discovered in our clinic on follow-up after a diagnosis of AION in the fellow eye. One patient was followed because of a question of amiodarone-induced optic neuropathy.

The mean age of our cohort was 63 years (range 45-74 years). There were 16 men and 7 women. Diabetes mellitus was present in 19 (83%) patients, 4 of whom were being treated with insulin. Among the 19 patients with diabetes, 11 had no evidence of diabetic retinopathy. Among the eight patients who had diabetic retinopathy, it was always nonproliferative. Systemic hypertension was present in 11 (48%). Four patients (17%) were being treated with...
amiodarone for cardiac arrhythmia; 3 of them also had diabetes. Only 2 patients were free of atherosclerosis. History and findings suggesting old AION in the fellow eye were present in 10 (43%) patients. Bilateral asymptomatic disc edema was present in 2 patients. The cup-to-disc ratio exceeded 0.2 in only 1 patient.

All patients underwent a complete ophthalmological examination, including visual acuity, biomicroscopy, pupillary tests, color vision tests, humpodiscopy, and visual field examination (Humphrey 30-2 or 24-2). Blood samples for glucose, urea, cholesterol, triglycerides, blood count, and erythrocyte sedimentation rate were drawn in all patients.

Fluorescein angiography, performed in all patients to distinguish congenital optic disc edema from acquired edema, demonstrated abnormal staining of the involved disc in every case.

All patients had a corrected visual acuity of 20/40 or better in the eye with asymptomatic optic disc edema. Depression of visual acuity was always attributable to cataract or diabetic retinopathy. There was no relative afferent pupillary defect on the side with the disc edema. Color vision was always normal. In eyes with asymptomatic optic disc edema, there was no visual field defect other than an enlarged blind spot.

Six patients underwent computed tomography of the brain when papilledema was considered, and none had pertinent abnormalities. A temporal artery biopsy in 1 patient with an erythrocyte sedimentation rate of 70 mm/h was normal.

Patients were followed on a weekly basis for the first month, then on a monthly basis until 1 of 2 endpoints was reached: 1) complete resolution of the optic disc edema with preserved visual function, or 2) development of AION, defined by subjective visual loss and visual field defect with or without decreased visual acuity, color vision, or afferent pupillary defect.

RESULTS

Table 1 summarizes the demographic parameters, systemic medical features, current drug therapy, and clinical endpoints of eyes with asymptomatic disc edema.

In 9 (36%) eyes, disc edema progressed to overt AION with sudden and persistent loss of vision. In these eyes, the mean time lag between the identification of the asymptomatic disc edema and the development of AION was 16.8 weeks (range 2–80 weeks). If the 1 patient who developed AION after 80 weeks (Patient 16) is excluded, the mean time lag for development of AION was 9 weeks (range 2–18 weeks).

Optic disc edema resolved without visual loss in 16 (64%) of eyes. In these eyes, the mean time for resolution of the optic disc edema was 15.5 weeks (range 4–44 weeks).

Among 10 patients (43%), history and ocular findings were consistent with the diagnosis of AION in the fellow eye. In this group, 4 (40%) demonstrated progression to overt AION, and 6 (60%) demonstrated resolution of the edema without visual loss.

The conversion rate to AION in other subgroups was 6 (31%) of 19 patients with diabetes, 3 (43%) of 7 patients with diabetic retinopathy, and 0 (0%) of 4 patients treated with amiodarone. Among 2 patients with binocular asymptomatic disc edema, 1 patient progressed to AION in both eyes, and the other patient had 1 eye resolve without visual loss and the fellow eye develop classic AION.

Among the 9 eyes that progressed to AION, the mean visual acuity was 0.63 log Mar (range 0.2–1.3). Among the 6 eyes who underwent threshold visual field testing after converting to AION, the mean of the mean deviation was –15.3 dB (range –8.1 to –27.7 dB).

DISCUSSION

Our study found that asymptomatic disc edema resolved without visual loss in 64% of eyes with a mean latency of 15.5 weeks (range 4–44 weeks). In 36% of eyes, optic disc edema progressed to AION with a mean latency of 16.8 weeks (range 2–80 weeks). Among those who progressed to AION, most had diabetes mellitus, but the rate of progression to AION was not dependent on the presence of diabetic retinopathy, nor did a history of AION in the fellow eye predispose to the conversion to AION in the asymptomatic eye.

Our study is the first to prospectively follow a sufficient number of patients with asymptomatic disc edema to estimate the rate of developing AION in these patients, as well as the latency of conversion.

The optic disc edema in this group of patients may represent a state of disc ischemia not severe enough to cause loss of axonal function. AION is associated with systemic diseases such as hypertension, diabetes mellitus, and atherosclerotic cardiovascular and cerebrovascular disease (6–9). The fact that all but two of our patients had systemic diseases that are associated with atherosclerosis suggests that asymptomatic optic disc edema may be a preinfarctive state in these patients. Almost half of our patients had past AION in the fellow eye, suggesting that their asymptomatic disc edema may be considered an impending AION. Another argument to imply that asymptomatic disc edema in these patients is related to ischemia and AION was the small cup-to-disc ratio in all but one of them (10).

We were surprised at the high prevalence of diabetes (83%) in our group. It could be argued that the asymptomatic disc edema was incidentally discovered in patients with diabetes because they undergo regular fundus examinations, but we have not observed this entity as frequently in other groups of patients who undergo comparable periodic

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.
<table>
<thead>
<tr>
<th>Pt. no/age/gender</th>
<th>Systemic diseases</th>
<th>Diabetes treatment/ amiodarone</th>
<th>Optic disc abnormalities</th>
<th>Visual acuity at presentation</th>
<th>Time to resolution or AION</th>
<th>Final visual acuity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/67/F</td>
<td>Diabetes, hypertension</td>
<td>Diet</td>
<td>RE: Edema</td>
<td>20/30</td>
<td>Resolved 9 wks</td>
<td>20/25</td>
</tr>
<tr>
<td>2/70/M</td>
<td>Diabetes, stroke, PAF, renal tumor, hypertension</td>
<td>Oral hypoglycemicins, amiodarone</td>
<td>RE: Edema</td>
<td>20/30</td>
<td>Resolved 13 wks</td>
<td>20/30</td>
</tr>
<tr>
<td>3/70/F</td>
<td>Diabetes</td>
<td>Oral hypoglycemicins</td>
<td>RE: Pallor</td>
<td>20/50</td>
<td>AION 6 wks</td>
<td>20/40</td>
</tr>
<tr>
<td>4/49/M</td>
<td>Diabetes</td>
<td>Insulin</td>
<td>RE: Pallor</td>
<td>20/40</td>
<td>Resolved 4 wks</td>
<td>20/25</td>
</tr>
<tr>
<td>5/74/M</td>
<td>Diabetes, PAF, hypertension</td>
<td>Oral hypoglycemicins, amiodarone</td>
<td>RE: Edema</td>
<td>20/20</td>
<td>Resolved 5 wks</td>
<td>20/20</td>
</tr>
<tr>
<td>7/66/F</td>
<td>Diabetes</td>
<td>Oral hypoglycemicins</td>
<td>RE: Normal</td>
<td>20/40</td>
<td>Resolved 9 wks</td>
<td>20/40</td>
</tr>
<tr>
<td>8/66/M</td>
<td>Diabetes, arrhythmia</td>
<td>Oral hypoglycemicins, amiodarone</td>
<td>RE: Pallor</td>
<td>20/400</td>
<td>Resolved 4 wks</td>
<td>20/25</td>
</tr>
<tr>
<td>9/73/F</td>
<td>Diabetes</td>
<td>Insulin</td>
<td>RE: Edema</td>
<td>20/20</td>
<td>AION 4 wks</td>
<td>20/200</td>
</tr>
<tr>
<td>10/84/M</td>
<td>—</td>
<td>—</td>
<td>RE: Edema</td>
<td>20/20</td>
<td>AION 2 wks</td>
<td>20/40</td>
</tr>
<tr>
<td>11/64/M</td>
<td>Diabetes, hypercholesterolemia</td>
<td>Diet</td>
<td>RE: Edema</td>
<td>20/20</td>
<td>Resolved 9 wks</td>
<td>20/20</td>
</tr>
<tr>
<td>12/68/M</td>
<td>Hypertension, PAF</td>
<td>Amiodarone</td>
<td>RE: Pallor</td>
<td>20/25</td>
<td>Resolved 28 wks</td>
<td>20/25</td>
</tr>
<tr>
<td>13/53/F</td>
<td>Hypertension, PAF</td>
<td>—</td>
<td>RE: Pallor</td>
<td>20/50</td>
<td>AION 4 weeks</td>
<td>20/30</td>
</tr>
<tr>
<td>14/61/M</td>
<td>Diabetes</td>
<td>Oral hypoglycemicins</td>
<td>RE: Edema</td>
<td>20/25</td>
<td>Resolved 9 wks</td>
<td>20/20</td>
</tr>
<tr>
<td>15/72/M</td>
<td>Diabetes, hypertension</td>
<td>Oral hypoglycemicins</td>
<td>RE: Edema</td>
<td>20/50</td>
<td>Resolved 28 wks</td>
<td>20/20</td>
</tr>
<tr>
<td>16/72/M</td>
<td>Diabetes, hypertension</td>
<td>Oral hypoglycemicins</td>
<td>RE: Edema</td>
<td>20/20</td>
<td>AION 80 wks</td>
<td>20/400</td>
</tr>
<tr>
<td>17/65/M</td>
<td>Diabetes hypertension</td>
<td>Oral hypoglycemicins</td>
<td>RE: Normal</td>
<td>20/30</td>
<td>Resolved 44 wks</td>
<td>20/50</td>
</tr>
<tr>
<td>18/61/M</td>
<td>Diabetes, stroke, hypertension</td>
<td>Oral hypoglycemicins</td>
<td>RE: Edema</td>
<td>20/20</td>
<td>AION 6 wks</td>
<td>20/400</td>
</tr>
<tr>
<td>19/47/F</td>
<td>Diabetes</td>
<td>Insulin</td>
<td>RE: Pallor</td>
<td>20/70</td>
<td>Resolved 5 wks</td>
<td>20/20</td>
</tr>
<tr>
<td>20/52/F</td>
<td>Diabetes</td>
<td>Insulin</td>
<td>RE: Edema</td>
<td>20/30</td>
<td>AION 18 wks</td>
<td>20/50</td>
</tr>
<tr>
<td>21/54/M</td>
<td>Diabetes hypertension</td>
<td>Oral hypoglycemicins</td>
<td>RE: Edema</td>
<td>20/20</td>
<td>RE: Resolved 6 wks</td>
<td>20/20</td>
</tr>
<tr>
<td>22/70/M</td>
<td>—</td>
<td>—</td>
<td>RE: Normal</td>
<td>20/20</td>
<td>AION 14 wks</td>
<td>20/40</td>
</tr>
<tr>
<td>23/73/M</td>
<td>Diabetes, hypercholesterolemia, hypertension</td>
<td>Oral hypoglycemicins</td>
<td>RE: Normal</td>
<td>20/40</td>
<td>Resolved 9 wks</td>
<td>20/30</td>
</tr>
</tbody>
</table>

AION, anterior ischemic optic neuropathy; F, female; M, male; RE, right eye; LE, left eye; PAF, paroxysmal atrial fibrillation.
eye examinations, such as those with high myopia, previous retinal detachment, retinal artery or vein occlusion, age-related macular degeneration, or prior AION in one eye. In their case-control study, Jacobson et al (9) concluded that diabetes is a major risk factor for the development of nonarteritic AION. Moster (11) found as well that the vascular effects of diabetes contribute to nonarteritic AION. We therefore assume that the incidental finding of asymptomatic disc edema might be related, although not exclusively, to diabetes.

Diabetic papillopathy, first described in patients with juvenile-type insulin-dependent diabetes mellitus (12–15), is now recognized to occur in subjects with adult-onset non-insulin-dependent diabetes as well (2,16). In 1995, Regillo et al (2) found that all patients with diabetic papillopathy had at most only mild loss of vision, that their optic disc edema generally resolved after a few months without permanent severe visual loss, and that most had small cup-to-disc ratios. However, these authors excluded patients who developed AION, a fact that could artificially separate diabetic papillopathy from AION. We believe there is much similarity between our group of patients and those described in the past as having diabetic papillopathy. Perhaps such patients actually have an asymptomatic disc edema that has not evolved into full-blown AION.

REFERENCES
Pituitary Apoplexy Causing Optic Neuropathy and Horner Syndrome Without Ophthalmoplegia

Robert K. Shin, MD, Brett L. Cucchiara, MD, David S. Liebeskind, MD, Grant T. Liu, MD, and Laura J. Balcer, MD, MSCE

Abstract: A 47-year-old woman presented with headache, acute monocular vision loss, and ipsilateral Horner syndrome. Apart from the optic neuropathy, all cranial nerve function was intact. Magnetic resonance imaging revealed an enlarged pituitary gland with compression of the orbital apex. The surgical specimen was consistent with pituitary apoplexy. The combination of headache, acute visual loss, and ipsilateral Horner syndrome without ophthalmoplegia, which may suggest carotid artery dissection, is evidently an unusual manifestation of pituitary apoplexy.

(Pituitary apoplexy, the sudden enlargement of a pituitary tumor, is a rare but potentially life-threatening condition. It is highly variable in presentation but is typically characterized by sudden headache, vision loss, and ophthalmoparesis and is generally associated with either tumor infarction or hemorrhage (1,2). The visual abnormalities, if monocular, may mimic retrobulbar optic neuritis (3). Oculomotor nerve palsies occur in more than 50% of patients with pituitary apoplexy, but trochlear and abducens palsies, or even complete ophthalmoplegia, can occur as well (4). These ocular motor findings may be unilateral or bilateral. We describe a patient with acute monocular vision loss and painful Horner syndrome, with no impairment of extraocular movements, as an unusual presentation of pituitary apoplexy.

CASE REPORT

A 47-year-old woman awoke with "blurry vision" in the OS and a headache over her left forehead and temple. She presented the following day to the ophthalmology clinic. Her past medical history was significant for hypertension, congestive heart failure, and a left ventricular apical thrombus. She had no prior ophthalmologic history. The patient's medications included lisinopril (Zestril), furosemide (Lasix), digoxin, and warfarin (Coumadin). She had a history of tobacco use and admitted to poor compliance with her medications.

On examination, visual acuities were 20/15 OD and hand motions OS. The pupils were equal, measuring 4 mm in diameter in dim illumination. There was a brisk consensual response to direct light stimulation OD to 2 mm. A prominent (3+) relative afferent pupillary defect was present OS. The patient perceived 14/15 Ishihara color plates with the OD but could not see the control color plate with her left. Extraocular movements were full. Slit-lamp examination and ophthalmoscopy were normal. Confrontation visual field testing was normal in the OD but revealed dense central and inferior altitudinal defects in the OS.

Computed tomography showed no evidence of intracranial hemorrhage, but the sella was noted to be "top normal" in size. She was found to be suboptimally anticoagulated (INR = 1.2). Several hours later, the patient developed 2 mm of ptosis OS, 1 mm of lower lid elevation OS, and anisocoria (pupillary diameters 6 mm OD, 3 mm OS in darkness). She continued to demonstrate a brisk consensual response to light stimulation OD. Pupillary dilation, however, was sluggish OS. There was no loss of facial sensation, corneal reflexes were intact bilaterally.

Magnetic resonance angiography of the neck and head showed no evidence of carotid artery dissection, and echocardiography found no trace of her previously identified left ventricular thrombus. Magnetic resonance imaging revealed a 2 cm sellar mass consistent with a pituitary adenoma. Magnetic resonance imaging showed no evidence of carotid artery dissection, and echocardiography found no trace of her previously identified left ventricular thrombus. Magnetic resonance imaging revealed a 2 cm sellar mass consistent with a pituitary adenoma. Magnetic resonance imaging showed no evidence of carotid artery dissection, and echocardiography found no trace of her previously identified left ventricular thrombus. Magnetic resonance imaging revealed a 2 cm sellar mass consistent with a pituitary adenoma. Based on the acute clinical presentation and magnetic resonance imaging findings of a large sellar mass, the patient was diagnosed with pituitary apoplexy. She received high-dose corticosteroid treatment and underwent transsphenoidal resection of the tumor. Pathologic findings were consistent with bland infarction of a pituitary adenoma.)
FIG. 1. Enhanced coronal T1-weighted magnetic resonance imaging scan shows asymmetric peripheral enhancement (black arrow) of a 2 cm sellar mass. The left optic nerve (white arrowhead) can be seen adjacent to the area of enhancement and slightly indented.

Following surgical decompression of the tumor, the patient’s headache resolved and visual acuity OS improved to 20/40 within 5 days. One year later, her visual acuity was 20/25 OS. Mild left optic nerve pallor and a small inferior nasal field defect to confrontation (confirmed by automated perimetry) remained. There was no residual ptosis or anisocoria.

DISCUSSION

Our patient’s unusual combination of acute optic neuropathy and painful Horner syndrome in the absence of ocular motility findings emphasizes the range of presentations of pituitary apoplexy.

We can explain this combination of findings by considering the anatomy of the cavernous sinus and orbital apex. Postganglionic oculosympathetic fibers travel within the wall of the internal carotid artery into the cavernous sinus. Within the cavernous sinus, oculosympathetic fibers travel briefly with the abducens nerve (VI), and ultimately join the ophthalmic nerve (V1) (5). Although the combination of Horner syndrome with pain in a trigeminal distribution might suggest a lesion in the cavernous sinus (6), such a localization would not account for the presence of visual loss. Moreover, because the ophthalmic nerve (V1) lies in the inferolateral wall of the cavernous sinus (Fig. 2A), it would be unlikely for an expanding pituitary mass to affect it in the cavernous sinus while sparing the adjacent ocular motor nerves (III, IV, and VI).

More anteriorly, however, the ophthalmic nerve (V1) travels superiorly and medially as it approaches the orbital apex. The nasociliary branch of V1 enters the orbit through the medial aspect of the superior orbital fissure, carrying oculosympathetic fibers to the pupil dilator (Fig. 2B). A pituitary mass could expand laterally and anteriorly to

FIG. 2. A: Schematic coronal view of the left cavernous sinus. Cranial nerve V1 lies in the inferolateral wall. The dotted line demonstrates the location of our patient’s pituitary mass with impingement on the left internal carotid artery wall and sympathetic fibers. B: Schematic coronal view of the left superior orbital fissure and annulus of Zinn. Note that the nasociliary branch of V1 travels medially, closest to the optic nerve. In our patient, the optic nerve and nasociliary branch of V1 were likely compressed by tumor at the intracranial exit from the optic canal. Adapted with permission (13).

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.
compress both the optic nerve and the oculosympathetic fibers of the nasociliary nerve at the orbital apex, parsimoniously explaining the concurrence of optic neuropathy and oculosympathetic deficit in the absence of ocular motor palsies in our patient. Compression of the superior portion of the optic nerve against the dural shelf of the optic canal, which can occur when the optic nerve is elevated by tumor, may also provide an anatomic explanation for the inferior location of our patient's monocular visual field loss (7). As the combination of optic neuropathy and Horner syndrome has not, to our knowledge, been previously reported in the setting of pituitary apoplexy, it must be rare.

As a cause of painful Horner syndrome, cervical or intracavernous carotid artery dissection is more common than pituitary apoplexy. In one report, painful Horner syndrome was present in 44% of patients with extracranial internal carotid artery dissection (8). In such cases, the oculosympathetic deficit originates at the site of dissection, where postganglionic fibers traveling within the wall of the carotid artery can be interrupted. Transient monocular vision loss or ischemic optic neuropathy may accompany the Horner syndrome in this setting (9). The vision loss results from embolism or reduced blood flow to the retina or optic nerve. Periorbital, brow, and scalp hypesthesia and pain may occur in the setting of carotid dissection (10).

Two mechanisms have been suggested to explain these manifestations (11). In the case of intracavernous carotid artery dissection, compression of V1 trigeminal fibers may occur; in the case of cervical carotid artery dissection, damage occurs to V1 trigeminal afferent fibers due to microembolization of nutrient arteries supplying the trigeminal nerve (12).

Thus, the triad of optic neuropathy, trigeminal dysfunction, and Horner syndrome is hardly specific to orbital apex lesions. Carotid artery dissection must be ruled out in any patient, particularly if there are signs of inadequate optic nerve or retinal perfusion or retinal emboli on funduscopic examination.

REFERENCES
Irreversible Blindness Due to Multiple Tuberculomas in the Suprasellar Cistern

Kumudini Sharma, MD, Sunil Pradhan, MD, DM, Atul Varma, MS, and Bharti Rathi, MD

Abstract: A 14-year-old girl developed fever, severe headache, vomiting, and no light perception in both eyes over a 3-day period without a previous complaint of visual or other neurologic difficulties. Neuro-ophthalmologic examination was normal apart from meningismus and blindness. Brain imaging showed ventriculomegaly and multiple enhancing nodules around the optic chiasm. Lumbar puncture showed an elevated opening pressure with lymphocytic pleocytosis. Polymerase chain reaction and enzyme-linked immunoabsorbent antibody tests on the cerebrospinal fluid were positive for Mycobacterium tuberculosis. There was no evidence of tuberculosis elsewhere in the body. Standard antituberculous treatment, including corticosteroids, did not reverse the blindness.

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

A 14-year-old girl experienced holocranial headache, body ache, fever, and vomiting for 2 weeks. Thereafter she noticed progressive visual loss in both eyes leading to complete blindness in 3 days and a single generalized seizure. There was no history of skin rash, joint pain, camping in the woods, or contact with tuberculosis. The daughter of a physician, she had had no prior visual or constitutional symptoms.

She was conscious and cooperative but had no perception of light in either eye. Ocular movements were full; pupils were semidilated and showed no reaction to light. Ophthalmoscopy was normal. Neck flexion and straight leg raising elicited neck pain, but otherwise the neurologic examination was normal. A hemogram was normal, but the erythrocyte sedimentation rate was elevated at 27 mm/hour. Standard blood chemistries were normal, as was a vasculitis profile. Serum IgM for *Borrelia burgdorferi*, smear for malaria, urinalysis, and chest radiograph were unremarkable. On lumbar puncture, cerebrospinal fluid (CSF) pressure was raised but not quantitated; CSF protein was 61 mg%, sugar was 7 mg%, and white blood cells were 175/mm³ (lymphocytes 95%). Cryptococcal antigen was negative. CSF smear was negative for acid-fast bacillus (AFB), capsulated bacteria, or fungus. CSF culture did not show any AFB or fungal growth. Mantoux test was positive, showing a 20-mm-diameter wheal with flare. Polymerase chain reaction and enzyme-linked immunosorbant antibody IgM for *Mycobacterium tuberculosis* were positive in CSF (38.5; normal less than 22).

Brain magnetic resonance imaging (MRI) revealed multiple nodular enhancing lesions in the suprasellar cistern; some lesions were solitary, while others show conglomeration, a finding consistent with tuberculosis (Fig. 1).

She was treated with a standard regimen of antituberculous medications (oral rifampicin 450 mg/d, oral isoniazid 300 mg/d, intramuscular streptomycin 1500 mg/day), oral prednisolone 1 mg/kg/d, and carbamazepine 600 mg/d. Because of the elevated intracranial pressure, oral acetazolamide 750 mg/d was also prescribed. Vision remained no light perception in both eyes, so a surgical tranfrontal “cleaning” of the chiasmatic cistern was performed at another institution. Six months later, she remains completely blind. Imaging has not been repeated.

DISCUSSION

A central nervous system infection with *M. tuberculosis* causes a granulomatous inflammatory reaction that involves the meninges and/or parenchyma. Visual symptoms in tuberculous meningitis are often due to optic neuritis (papillitis or retrobulbar neuritis) or opticochiasmatic arachnoiditis. The latter appears on MRI as basal meningeal thickening, often with contrast enhancement. Rarely may masses or tuberculomas form within or adjacent to intracranial portions of the optic nerve or optic chiasm (1,2). Multiple tuberculomas occupying the entire suprasellar cistern, as seen in our case, have not been described so far. Visual loss produced by tuberculomas is usually insidious in onset and gradually progressive. These lesions are to be differentiated from other inflammatory granulomas, including sarcoidosis, as well as lymphoma.

REFERENCES


The Vitality of the Pupil: A History of the Clinical Use of the Pupil as an Indicator of Visual Potential

H. Stanley Thompson, MD

It is obvious to neuro-ophthalmologists today that the reactivity of the pupil can serve as an indicator of an eye’s potential for vision, but it was not always so clear. This clinical association between pupillary mobility and vision has been recognized for at least 2000 years, so it is strange that it seemed to pop up in 20th century ophthalmic practice as if it were a new test.

ANCIENT MEDICINE

Like so many things in medicine, it started with Galen in the 2nd century (Fig. 1). Claudius Galenus came from Pergamum, which is now in western Turkey, but at that time it was part of the Roman Empire. He began the study of medicine at age 16 and then went on to work in the great medical centers of the day—Smyrna, Antioch, and Alexandria—before returning to Pergamum. Then he moved to practice in Rome, the power center of the world. He soon became famous. He was a forceful and opinionated man who did not make himself popular with other Roman doctors.

In his practice he crouched cataracts, as did many doctors, and like everyone else, some of his cataract patients were not helped by the surgery. If a patient came to Galen with a cataract in one eye, and asked him to fix it, he had, of course, the right to refuse to do the cataract coughing. A high success rate would, naturally, be good for his reputation, and nothing was to be gained by operating on an irretrievably blind eye, so he needed an indicator to predict the outcome of the surgery.

Galen must have noticed that he could not depend on a visible inequality of pupil size to decide whether the eye behind the cataract was sound. One eye or the other could be blind, either from the cataract or from something else, and still the two pupils could be of the same size.

He knew that the pupils were small when the eyes were exposed, and that they dilated when covered. His light source was the window, or the sky, and he controlled the light by putting a hand over one of the patient’s eyes (Fig. 2). He noticed that if, in a patient with good vision in both eyes, he put his hand over one eye, the pupil of the other eye would show a small but definite dilation. Galen’s explanation for this observation was that there was a substance that he called the “breath of vision” (“pneuma”) that came from the brain into the eye via the optic nerves. This pneuma served to keep the pupil wide as it emerged from the eye to mix with incoming external rays, thus facilitating the process of vision. When that eye was covered, the pneuma, finding itself no longer needed, went around, via the tubes of the chiasm, to the other eye to help it to see, and incidentally to dilate its pupil.

We would now call this dilation “consensual,” and we would explain it by saying that the input from both eyes was contributing to the pupil size, and if one eye were covered, this “pupillomotor input” would be reduced by 50%, and this would, in turn, reduce the “pupillomotor output” to both eyes by 50%, resulting in a small but visible dilatation of both pupils.

Interestingly, Galen went on to remark that he had noticed that if he put his hand over a blind eye—whether it had a cataract or not—the other pupil (the one that was still
H. Stanley Thompson was born and raised in China, the son of Irish missionaries. Educated in China and Ireland, he spent the years of World War II in a Japanese concentration camp in China. Following the war, his family emigrated to the United States from Belfast, Northern Ireland. He completed undergraduate work and medical school at the University of Minnesota. In 1962, he interrupted his University of Iowa ophthalmology residency to work in the pupillography laboratory of Otto Lowenstein, MD and Irene Loewenfeld, PhD at Columbia University. So fascinated was he by their research that he settled on a career in neuro-ophthalmology. On completing his residency at Iowa, he completed a 1-year neuro-ophthalmology fellowship from 1966 to 1967 under the tutelage of William F. Hoyt, MD, returning to the ophthalmology faculty at Iowa, where he remained director of neuro-ophthalmology until his retirement in 1997. During his 30-year tenure at Iowa, he trained 40 neuro-ophthalmology fellows and authored over 200 articles and countless book chapters. Acknowledged internationally as the "master of the pupil," he used instrumental inventiveness and relentless, precise clinical observation to redefine pupillary physiology and its clinical application to the afferent pupil defect, Adie's tonic pupil, pharmacologic assessment of Horner syndrome, and observations of bizarre phenomena such as tadpole pupils. His trainees still cling to coffee napkins covered with quaint Thompson sketches of neural pathways illustrating the workings of the brain. In retirement, he studies the history of ophthalmology, and with his wife Delores, tends sheep and manages an on-line bookstore specializing in the illustrators of children's books and the history of medicine.

visible to him) would not dilate (1). Today we would say, "Well, that's easy! It is because the blind eye was not contributing to the pupil size, so covering it up would make no difference."

It is fascinating that neither Hippocrates nor Galen ever stated the apparently obvious fact that the pupils constrict when exposed to light and dilate again when the light is withdrawn. I imagine that this was because Galen was still trying to fit his observations into Plato's scheme of things, and this involved a pneuma emerging from the eye, and it just didn't occur to him to cover the good eye and then cover and uncover the eye with the cataract.

Galen's great contribution to clinical medicine at this point was his willingness to set aside his philosophical speculations about the mechanisms at work, and to simply recommend using the mobility of the pupils as a prognostic sign when considering a cataract for surgery. He would just cover the cataractous eye and watch the pupil of the other eye. If it dilated, he would conclude that there was visual potential behind the cataract that he had just covered, and he would schedule the cataract surgery (2). The importance of this pupillary sign rests on the fact that it was an observable and objective indicator, independent of the patient's feelings about his visual loss, that it made a statement about the integrity of a part of the visual system that was otherwise entirely invisible and unknowable to the doctor.

Because Galen actually wrote down many of the things he was thinking about, his fame lasted long after his death in 199 CE. In addition, Rome was soon to be in decline and the invading barbarians swooped down again and again to pillage and destroy, and thus contributed to the suppression of intellectual activity in most of Western Europe. Some of Galen's writings were translated into Arabic and survived. In the long run, all this had the effect of making Galen even more famous, and his writings became so authoritative that as they aged they took on the aura of canon law, and disagreement was not permitted. Galen's opinions and recommendations became the high water mark of medical knowledge on this subject for hundreds of years.

**ARABIC MEDICINE**

During the early middle ages, Galen's prognostic pupillary sign for cataract couchers was repeated by many Middle Eastern medical authors writing in Arabic, but, because of translation and transcription errors, it was not always passed along intact (3,4). It was not offered as an indispensible test, and I'm not sure that it was always fully understood, because once the concept was accepted that it was the light entering the eye that caused the pupils to constrict, then just looking at the direct light reaction was easier to understand and easier to do than Galen's test.

In the 7th century, Paul of Aegina was saying that a large pupil was common in an eye with bad vision, and he
recommended rubbing both eyes through the eyelids in connection with checking the pupils. Soon the Greek idea that rays emerging from the eyes contributed to the process of vision had been abandoned, and it was clear to both Rhazes (865–925) in the 10th century and to Ammar Ibn Ali in the 11th century that the pupil was constricting in response to light entering the eye (5). This made it possible to think of Galen’s test as a rather roundabout way of evaluating the direct pupillary reaction of the cataractous eye to exposure to light.

RENAISSANCE MEDICINE

During the 16th century, European intellectual activity was experiencing a dramatic rebirth. In Venice, Galen’s work was translated for the first time from its original Greek straight into Latin, without going through Arabic. Greek and Latin versions of Galen’s works were then published by the Aldine Press in 1525, using moveable type.

The Swiss barber-surgeon Pierro Franco (1504–1578) specialized in hernias and cataracts. The most experienced and skilled cataract coucher of the 16th century, he had three criteria for judging the readiness of a cataract for the couching needle: 1) The color of the cataract (pearly white is best); 2) The degree of loss of vision (it should be severe); and 3) The pupillary mobility (it should be normal, despite 1 and 2 above). Franco asserted that:

One should rub the cataract-stricken eye a little, after first closing the other eye. If then the cataract expands and widens, and then returns to its previous status immediately (“upon lifting the lid” seems to be left unsaid) then that is an indicator that the eye is well suited for the operation, otherwise not (6).

Felix Platter was born in 1536 into a well-to-do family in Basel (Fig. 3). He had read Galen and various Arabian medical authorities when he was in medical school in Montpellier. Platter was the first to clearly state that the eye was an optical instrument, that vision did not take place in the crystalline lens, and that the lens served only to focus the light onto the retina, which, he believed, was an extension of the nervous system and the true percipient layer within the eye (6).

Platter compared a cataract to a tree-ripened fruit. If the surgeon would just wait until the cataract was “ripe,” he could save himself a lot of trouble, and eventually the cataract would fall easily from the tree into his waiting hands. For Platter, the color of a ripe cataract should be “like the skin that envelops the white of a cooked egg.” He also used pupillary reactivity as a sign of a “ripe” cataract (6).

Ambroise Paré was born into a French family of barbers, and his education was scanty. He knew no Greek or Latin (Fig. 4). At first he apprenticed to his brother, a barber-surgeon, and then moved to Paris to a similar position.
He worked as a house surgeon at the Hôpital Dieu, and then as a military surgeon. Since he was not taught to bow down to the ancient teachers, he learned to trust his own observations. For example, he quickly rejected the common practice of pouring boiling oil into a chest wound on the grounds that it did more harm than good. He taught surgeons to be gentle with tissue and he became the best-known surgeon of the 16th century. Pare's precataract pupil check was very similar to that of Pierro Franco, but more detailed and explicit.

Here is Ambroise Pare's comment, as translated at the time into Elizabethan English, on the "ripeness" of a cataract, under the heading "By what signs ripe and curable cataracts may bee discerned from unripe and uncurable ones":

If the sound eye being shut, the pupil of the sore or suffused eye, after it shall be rubbed with your thumbe, bee presently dilated and diffused, and with the like celerity returne into the place, color and state, it is thought by some to shew a ripe and confirmed cata­ract. But an unripe and not to be couched, if the pupil remain dilated and diffused for a long time after . . . .

Cataracts are judged uncurable . . . whose pupill becometh no broader by this rubbing: for hence you may gather that the stopping or obstruction is in the opticke nerve, so that how cunningly or well soever the cataract bee couched, yet will the patient remain blind (8).

All three of these 16th century surgeons—Franco, Platter, and Paré (6)—as well as Bartisch (7), recommended using the pupils as a predictor of visual success in cataract couching just as Galen had recommended 1300 years before, but their test was a little different and definitely easier to do. As the Arabian authorities had done, they closed both of the patient's eyes, and pressed and rubbed the eyes through the eyelids with their thumbs. This may sound like hocus pocus, but it gave the doctor an opportunity to palpate the orbits for prominence, resistance, or discomfort. It also helped the pupil testing by briefly dark adapting the eyes, and this probably strengthened the direct pupillary response to light that could be seen when one eyelid was suddenly lifted.

Notice that these Renaissance doctors, even though they had access to a fresh translation of Galen, did not choose to make clinical use of Galen's test. They were no longer burdened with the idea that some component of vision streamed out of every seeing eye towards the object of regard, so that they were able to just watch the direct pupillary reaction to light. On the strength of Paré's fame, checking the direct light reaction of the pupil became standard practice for all cataract surgeons. For the next 300 years,
doctors were taught to look at the direct reaction to light in the eye that was up for cataract surgery (19), rather than looking, as Galen had originally suggested, for a weak consensual dilation of the other pupil when the cataractous eye was covered.

It is interesting that Hieronymus Fabricius ab Aquapendente (1513–1619), professor of Anatomy at Padua, said that Father Paul of Venice (Pater Paulus Vencitus, or Paolo Scarfi, 1552–1623) was the one who had demonstrated to him that the pupils contract and dilate with variation in light intensity. Later Plempius (1648) gave Father Paul the credit for being the first to make this observation (5), which disregards centuries of Arabic medicine.

EIGHTEENTH CENTURY

By the 18th century, there seemed to be a better understanding of how pupillary signs could be of help to the practicing eye doctor. For example, Charles de Saint-Yves (1667–1733), in his textbook New Treatise on the Diseases of the Eyes (1722), a book that remained in print for more than 80 years, said, on the clinical value of pupil watching:

"I have noticed over and over again in my patients that the extent of the visual impairment closely matches the impairment of iris movement. In fact I have found that, without talking to the patient about the visual problem, I have been able to make a fairly good estimation of the quality of the patient's vision, based only on my examination of the pupillary movements (9)."

Now there is a very modern sounding voice!

William Porterfield (1696–1771) knew of the work of his Edinburgh colleague Robert Whytt (1714–1766), who recognized that the pupillary response to light had an afferent and an efferent arm in separate nerves. In 1759, Porterfield seemed to understand that Galen said was an example of consensual dilation of the pupil of the other eye when the cataract eye was closed, and that when both eyes were stimulated, more pupillary constriction was produced than when only one eye was exposed to light (10).

NINETEENTH CENTURY

Benjamin Travers (1783–1858), a prominent English surgeon, viewed the pupil as part of a muscular system. His 1820 book, A Synopsis of the Diseases of the Eye, stated that "...Its contractility is in proportion to the strength and perfection of the nerve of sense with which it is associated." (11).

Travers was voicing a very old concept that had become generally accepted during the 18th century (see Saint Yves above), namely, that there is a "proportionality" between the integrity of the optic nerve and the strength of the pupillary response. This proportionality, or something like it, may have even been brought up in about 1250 by the Franciscan encyclopedist Bartholomaeus Anglicus (12).

He was working in Paris when he wrote about vision and the pupil:


("Blindness is the deprivation of sight. An eye can be blind because of a defect in the eyeball itself, with the result that the pupil is no longer proportionate to the quality of vision in that eye. In fact, to see well, everything needs to be working properly: there must be an "appropriate proportionality" in the eye itself—in that the eyeball must be fit to accept the 'image'.")

By forcing this statement into modern idiom, I may have distorted what Bartholomaeus was trying to say in the 13th century. He might have simply been saying that in a good eye the pupil moves well, while in a bad eye it moves poorly. In this translation, the word "image" has been substituted for "visual spirit" even though Bartholomaeus knew nothing of optical images in the eye and may not have been able to distinguish in his thinking between "light reaching into the eye" and "sharp vision reaching into the eye." A cataract certainly spoils the image falling on the retina and impairs vision, but it blocks very little light. This might account in retrospect for the mysterious breakdown in a cataractous eye of the customary proportionality between the vitality of the pupil and the quality of vision, the anomaly that attracted Galen's attention.

ARE PUPIL SIGNS UNTRUSTWORTHY?

William Mackenzie (1791–1868) of Glasgow wrote a famous textbook that dominated English ophthalmology in the 1830s and 1840s. He found it necessary to warn his readers that sometimes the pupil would react well to light "in cases of total blindness," (13) and this began a long period of doubt about the trustworthiness of pupillary signs.

In 1855, Albrecht von Graefe, at the age of 27, was already the acknowledged leader of German-speaking ophthalmology, and in that year, just as the new ophthalmoscope was becoming popular, he warned ophthalmologists not to be in such a hurry with the dilating drops that they missed important pupillary signs (14). Von Graefe was particularly interested in using the pupil reactions to decide whether a patient was pretending to be blind in one eye. He accepted the fact that there often was doubt about the real cause of the visual loss and that there remained some uncertainty about the dependability of the pupil responses in some conditions, so he offered pupillary reactivity only as a confirmatory sign of good vision in the tested eye. This..."
cloud of doubt about the clinical reliability of pupillary signs continued to hang over the office and bedside use of pupillary reactivity for the next 50 years.

Nineteenth century ophthalmologists did know, in general, that the absence of a pupillary light reaction was a classic and important sign of true blindness, as Boerhaave had taught early in the 18th century, and many doctors were writing about the pupil. The German word for a poorly reacting pupil was *Pupillenstarre*, and when this “stiffness” or “rigidity” of the pupil was complete it was sometimes called *absolute Pupillenstarre*. If the pupil reacted poorly to light but well to a near stimulus, it was called *reflektorische Pupillenstarre*, and if the failure of the light reflex was due to an input (afferent) problem, it was called an *amaurotische Pupillenstarre*. Ludwig Bach’s 1908 344-page book *Pupillenlehre* seems almost bogged down by this terminology. Heddaeus (15), reaching for a better term for the afferent kind of pupillary defect, and making an analogy to another sensory input, suggested the term *Reflextaubheit*, or reflex deafness of the pupil. He championed this awkward term vigorously throughout the 1880s, but it was generally rejected. These lengthy discussions were mostly about terminology and they seemed to do very little for the clinician. Young ophthalmologists were still not taught to make daily use of the pupil as an indicator of vision.

In 1889, Ernst Fuchs (1851–1930) wrote a very influential textbook called *Lehrbuch der Augenheilkunde* that was widely used for the next 40 years. On the clinical pupillary examination he said only that “The reaction of the pupil to light is . . . used with great advantage to determine objectively whether an eye has any sensation of light or not (particularly in children, malingerers, etc.).” (16).

William Fisher Norris (1839–1901), son of a well-known Philadelphia surgeon, served in the Medical Corps of the Union Army in the American Civil War. He then spent 5 years (1865–1870) studying ophthalmology in Vienna with Mauthner, Arlt, and Jaeger. Upon return to Philadelphia, he soon became professor of ophthalmology at the University of Pennsylvania. William Pepper, Professor of Medicine at the University of Pennsylvania, put together a multivolume *System of Practical Medicine*, to which Norris contributed a chapter on medical ophthalmology. Strangely, in the 67 pages of his chapter, there is no mention of using pupillary reactivity as an indicator of the potential for vision in an eye (17).

In 1893, Norris and his student Charles Oliver wrote a one volume *Text-Book of Ophthalmology* (Lea Brothers, Philadelphia). This was so popular that they decided to edit a 4-volume, multiauthored *System of Diseases of the Eye* (1897–1900) (Fig. 5). In this set, there is a thoughtful chapter by S. Baudry of Lille on the subject of simulated blindness (18). Almost half a century after von Graefe’s comments on the value of the pupil’s reaction to light in cases of simulated blindness, very little had been added except that an eye with profound optic nerve dysfunction (“amaurosis”) shows more impairment of the pupillary light reaction than an eye with moderate optic nerve dysfunction (“amblyopia”), that the confusion between these entities and nonorganic (“hysterical”) visual loss and suppression amblyopia (“amblyopia ex anopsia”) was producing more diagnostic uncertainty and anxiety than ever, and that the clinical examination of the pupils was not any further advanced.

Charles Oliver’s own little 1895 book on how to examine the eye for optic nerve disease would be expected to have something about the pupillary examination, but this is all he had to say: “The two (eyes) are then to be covered and alternately exposed to the entering light stimulus until surety is made that there is muscular response or not.” (19). Nothing new since Ambroise Paré!

The long legacy of writings about the pupil had apparently had little impact on the routine examination of the eyes. Some 1800 years earlier, Galen had insisted that the two pupils worked together when one eye was covered, and he had applied this observation to the indications for cataract surgery. Some 200 years before the publication of Norris’ textbook, Saint-Yves had been saying that looking at the pupillary responses should be an early part of every eye examination, and yet somehow this part of the examination had fallen into disfavor in the 19th century. Why?

I believe that this apparent lapse was the natural result of the steady accumulation of knowledge. As new clinical observations were confirmed, it became possible to ask...
some difficult questions about the pupils, but the details of the anatomy and physiology of the pupillary light reflex were not fully understood until late in the 19th century. Without these details, it was hard to account for some of the observed pupillary behavior. There seemed to be too many exceptions to make it a dependable tool.

What kind of exceptions are there to cast doubt upon the ancient rule that pupil reactions and remaining vision always go hand in hand?

1. There were some patients with good vision whose pupils reacted weakly to light or not at all. Patients with one fixed pupil could have vision that was less than perfect; trauma or iritis could have damaged the iris; and in younger patients, denervation of the iris sphincter usually also induced visual complaints at near. These “efferent” (pupillomotor output) problems such as third nerve palsies, Adie pupils, and atropinic drug responses generally resulted in a pupil with a weak light reaction on the affected side, and this produced a pupillary inequality that increased with the brightness of the light. By the middle of the 19th century it was recognized that these patients usually had good vision even when looking through a large or unreactive pupil. In fact, this had been clearly stated by Platter in the 16th century (20).

Sometimes an eye that could read the 20/20 line had a clinically visible impairment of the direct light reaction, compared with the response when the other eye was stimulated. Some of these eyes were found to have a considerable loss of peripheral visual field, which accounted for the loss of pupillomotor input.

2. An eye with poor vision would sometimes seem to have perfectly normal pupil responses to light (21). Of course, many allegedly blind eyes were not truly blind. For example, eyes with very poor vision due to a large central scotoma or a deep suppression amblyopia, or with nonorganic visual loss, seemed to have good, or at least reasonably good, pupillary responses. This was because most of the retina was still in good working order and properly wired up to the midbrain. An effort was made to dodge this problem by reducing the clinical examination of the pupillary light reactions to a “yes” or “no” question where any consistent response to light was accepted as a normal response. This added to the difficulties. It should be noted that in the late 19th century there were still very few eye doctors who actively set out, in their examination of the patient, to compare the direct light reaction in the two eyes.

Occasionally, the pupil of a truly blind eye could be seen to constrict during the examination and an “eyelid-closure pupillary constriction” (thought to be a stray near response) was not recognized (22).

If a bright slit-lamp beam shines directly upon a truly blind eye, a definite light reaction can sometimes be seen, and the examiner may never suspect that the light is being reflected off the patient’s face and then off the examiner’s white coat and thence into the patient’s other eye—an eye that is sound, dark adapted and, at that moment, exquisitely sensitive to light.

When von Graefe wrote in the 1850s of using the pupillary light reaction to distinguish a real optic neuropathy from the simulation of blindness, he brought up the possibility that a patient could have a stroke or an injury that would damage the visual cortex and make the patient “cortically blind” without damaging the pupillary light reflex to and from the midbrain, so that the patient would retain normal pupillary responses to light (14). A generation later, when autopsies were more common, this became well established (23).

In the hope of explaining some of these mysterious exceptions to the old rule that vision and pupil responses should go hand in hand, it was speculated that the pupillary afferent pathways and the visual pathways, although adjacent, were actually fundamentally different and responded differently to injury and disease. Either the pupillary fibers...
were thicker and more resistant to injury, or they were in separate fascicles and followed a slightly different path. These suggestions were never firmly proven, but a considerable literature was generated for many years (24) that may have diverted attention from the clinical use of pupillary signs in optic nerve disease. The matter of whether the pupillary light reaction is served by different ganglion cells with different properties and different receptive fields is still under discussion (25,26).

At the very beginning of the 19th century, anticholinergic mydriatics had been suggested by Karl Himly for use in cataract examination. In 1851, when the ophthalmoscope arrived on the scene, atropine was already in clinical use in cataract surgery and in iritis, so it was now used to open up the iris for this wonderful new view of the depths of the eye. This may have been another factor that contributed, in the last half of the 19th century, to the fall of pupillary observations into a secondary position in the routine eye examination: occasionally the professor wanted to look at the fundus without delay. Even though von Graefe had, in 1855, expressly warned against skipping the early careful examination of the pupils, his advice was not always taken, partly because in the same paper he admitted that the pupillary reaction to light was not an altogether trustworthy indicator of visual potential.

TWENTIETH CENTURY
Towards the end of the 19th century, confidence in the dependability of the pupil responses was growing. In
1884, Julius Hirschberg, the historian of ophthalmology, considered it worthwhile to publish a case report of a 17-year-old girl with recent unilateral visual loss (27). He had been able to say with confidence that the patient was not just pretending to be blind because he could see that her pupils failed to react well when the affected eye was stimulated with light. This degree of confidence was not shared by most eye doctors.

In 1901, Elia Baquis of Livorno also spoke of the value of a careful pupil examination in cases of suspected nonorganic visual loss, and emphasized comparing the direct and consensual reactions of the 2 eyes (28).

Vössitus also made good use of pupillary signs in a compensation case in 1906 (29).

Hirschberg remarked in 1901 that one of the oldest clinical observations ever made about the pupils was seldom mentioned in modern ophthalmic texts. He was referring to Galen’s observation about the behavior of the other eye. He demonstrated, in a series of patients and normal subjects, that the dilation of the uncovered eye could indeed be seen and was worth watching for (30). William Porterfield had made a similar observation in 1759 after reading Galen (10).

Robert Marcus Gunn (1850–1909) was a well-known London ophthalmologist, a careful cataract surgeon, and an observant ophthalmoscopist (Fig. 6). He described “Gunn’s dots” (bright points near healthy discs, that he always called “Crick Dots” after the family in which he first noticed them), “Gunn’s sign” (arteriovenous nicking of the retinal vessels), and “Gunn’s jaw-winking phenomenon.” Gunn went out of his way in 1897, and again in 1902 (31), to get his fellow ophthalmologists to pay attention to pupil responses as a sign of real optic nerve disease. Gunn emphasized the clinical value of the pupillary response to light in recognizing nonorganic visual loss and the inability of the pupil of the defective eye to maintain the contraction under direct exposure to light. He repeated these statements in a paper at the 1902 meeting of the British Medical Association on the recognition of nonorganic blindness that was published in Ophthalmic Review in 1904:

It is not sufficient to find that it (the pupil of the affected eye) contracts well or fairly well on exposure; the eye

![FIG. 10. Otto Löwenstein (1952).](image)

![FIG. 11. The Tilt Test: Using a neutral density filter to confirm a “threshold” afferent pupillary defect. In (A) and (B), a 0.3 log neutral density filter is held over the OS of a normal subject while the light is alternated from one eye to the other. It can be seen that both pupils constrict more in (A) when the light is brighter, i.e., without the filter. In (C) and (D), the filter is moved to cover the subject's OD, and again a small relative afferent defect can be seen when the shaded eye is stimulated (D). This “tilting” of the relative afferent defect by the same amount in each direction can be used to confirm a small input defect of clinical significance, because a 0.3 filter over the apparently affected eye will make a real asymmetry much larger, and the same 0.3 log filter over the other eye should make a real asymmetry disappear.](image)
must be kept under the direct stimulation of light and the pupil watched, as to whether it shows that secondary dilatation under continued exposure that is found associated with the amblyopia of retro-ocular neuritis."

He went on to remind his audience that both pupils showed this "secondary dilatation" (later called "pupillary escape") when the affected eye was stimulated, whereas the same light held on the normal eye would keep both pupils down.

Gunn was clearly stimulating one eye and then the other, but he does not tell us about the nature, intensity, and duration of the light stimulus used. Perhaps he merely had the patient look out of the window while he alternated the cover, but he does not report this. In his later writings, he was impressed that the pupils would constrict when the good eye was illuminated, and would ('paradoxically') dilate when the bad eye was illuminated. This statement, all by itself, suggests that he had started to alternate the cover.

In 1904, at a British Medical Association discussion on "retro-ocular neuritis," (33) Gunn and others only briefly mentioned the pupils as if it were well known that the pupils could be used to distinguish retrobulbar neuritis from non-organic visual loss. When printed in the Ophthalmic Review in 1905, the comment was "the pupil reaction is invariably impaired when there is even moderate amblyopia from neuritis, while it remains normal in cases of functional origin." (34) No mention was made of the pupillomotor escape-under-steady-illumination phenomenon. Getting ophthalmologists to incorporate this test into their routine examination must have been an uphill battle. When Gunn died in 1909 at age 59, the obituaries were filled with praise for his personality and his work, but no one mentioned any of his contributions to the examination of the pupils.

Alfred Kestenbaum came to America in 1939, bringing with him his skills in neuro-ophthalmology (Figs. 7, 8). In 1946, more than 40 years after Gunn, he offered two ways to demonstrate the existence of an asymmetry of pupillomotor input: (35)

1. With the patient in the light, he covered first one eye and then the other, remarking on the dramatic difference in the response between the good eye and the bad eye. He called this a "Modified Marcus Gunn Pupillary Sign."

2. Using a small pupil gauge or ruler, he measured the diameter in millimeters attained by each pupil in diffuse bright light when the other eye was firmly covered. Assuming that the pupils were equal in size when both were uncovered, the eye with the larger pupil (the weaker direct light reaction) had the relative afferent pupillary defect. He called this finding the "pseudaisocoria sign."

He also offered a way to roughly quantify the difference in pupillomotor input between the two eyes. He did this simply by subtracting these two pupil diameters. The resultant number, in millimeters, is an expression of the difference in pupillomotor input between the two eyes, because the pupillomotor output is assumed to be the same for OU. Hike to call this "Kestenbaum's Pupil Number" to avoid using the distracting word "pseudo-anisocoria." Even though this number is in millimeters, it roughly corresponds to the relative afferent pupillary defect measured in log units of neutral density filter (36).

It is interesting to note here that, starting with Galen, the emphasis in this part of the eye examination was to check the vigor of the pupillary reactions of one eye as the lighting conditions were varied. Sometimes the other eye was examined in a similar manner, and sometimes the pupil responses were compared from memory. Kestenbaum emphasized the clinical value of knowing the difference in pupillomotor input between the two eyes. He was the first to offer a simple way to attempt the quantification of this difference in the clinical examination.

In 1959, Paul Levatin (37) made a very important contribution (Fig. 9). He noticed that moving a hand-light (rather than a cover) quickly across the nose from one eye to the other seemed to bring out an asymmetry of pupillary input between the eyes. He called it the "swinging flashlight test." With this quick switch of the light stimulus from one eye to the other, the consensual dilation of the pupil in the second eye that resulted from taking the light away from the first eye was algebraically summed with whatever pupil constriction was generated by the light arriving at the second eye. Switching the light from one eye to the other thus amplified any difference in their pupillary contraction to light, and made that difference easier to see. Levatin knew Lowenstein and Kestenbaum and built on their contributions by focusing on the difference between the two eyes, by turning the alternating cover pupil test into an alternating light test, and by echoing Kestenbaum's observation that alternating the light between the two eyes seemed to amplify this difference. This made it possible to answer a question about asymmetry of pupillomotor input with a simple "yes" or "no"; it was no longer necessary to enter into a confusing discussion of direct and consensual reactions.

Otto Lowenstein (1890–1965), a neuropathologist with an interest in understanding the pupils by recording their actions, also came to America in 1939 (Fig. 10). He noticed that the shape of the pupillary tracing in an eye with optic nerve disease had a characteristic shape and behavior (a longer latency, less amplitude of movement, a lower peak speed attained) and that these features could be reproduced in a normal eye by just reducing the intensity of the stimulus light (38).

From these observations, it followed that in unilateral optic nerve disease, it might be possible to dim the stimulus to the better eye with a neutral density filter until the pupillary responses to light seemed visibly matched in the two eyes.
The density of the filter would then be a measure of the asymmetry of pupillomotor input between the two eyes (39).

PERSONAL RECOLLECTIONS

In 1963, after spending some time with Lowenstein and Loewenfeld in New York, one of the things that impressed me about trying to use pupillary reactivity to estimate the visual potential in an eye was the odd disparity between what people said and what people did. Everyone acknowledged that the mobility of the pupil was an indicator of residual vision, and that this had probably been known for millennia, but in the 1960s very few ophthalmologists seemed to be making daily use of the sign, with the exception of Kestenbaum, Levatin, Lawton Smith, John Stanley, Robert Drews, and their students. Edward Fineberg, of Miami, stirred me into adding neutral density filters to my regular clinical toolbox (40). The filters made it possible to quantify the asymmetry of pupillomotor input while using Levatín’s alternating light test.

Aki Kawasaki and Randy Kardon have pointed out that this asymmetry of pupillomotor input is not an absolutely stable quantity (41). Even when the asymmetry is carefully measured in normal subjects with a sophisticated instrument, under stable conditions, the amount of asymmetry seems to fluctuate a bit, so that an apparent 0.2 log asymmetry may sometimes turn out to be within the normal range (Fig. 11).

Looking carefully at the past is sometimes quite humbling because there were people centuries ago who made some amazing leaps of the imagination when there was little but intellectual rubble around their ankles. When almost every “discovery” turns out to be a rediscovery, our modern clinical contributions begin to seem like just an accumulation of observations.

REFERENCES

5. König E. La reazione pupillare come elemento diagnostico differenziale. ZentralblattPraktische Augenheilkunde 1905;24:335–8. See also Brandt’s 15th ed. under “reaction, eye-clinical pupils.”
6. Hirschberg J. On the Usefulness of the Parts, Book 7, Chap 19:196 (from a fascimile of a 1601 reprint, Frankfort.)
The Multifocal Electroretinogram

Donald C. Hood, PhD, Jeffrey G. Odel, MD, Candice S. Chen, MD, and Bryan J. Winn, BA

Abstract: The multifocal electroretinogram (mfERG) technique allows local ERG responses to be recorded simultaneously from many regions of the retina. As in the case of the full-field ERG, the ganglion cells contribute relatively little to the response, which originates largely from the outer retina. The mfERG is particularly valuable in cases in which the fundus appears normal, and it is difficult to distinguish between diseases of the outer retina and diseases of the ganglion cells and/or optic nerve. The mfERG can also help to differentiate among outer retinal diseases, to follow the progression of retinal diseases, and, with the addition of the mfVEP, to differentiate between organic and nonorganic causes of visual loss. However, because the difficulties encountered in recording and analyzing mfERG responses are greater than those involved in full-field ERG testing, mfERG testing is best left to centers with an electrophysiologist familiar with the mfERG test. Although this technique is relatively new and standards are still being developed, centers capable of recording reliable mfERG responses can be found in hundreds of locations around the world.


WHAT IS THE MULTIFOCAL ELECTRORETINOGRAM?

The electroretinogram (ERG) is a mass potential, the result of the summed electrical activity of the cells of the retina. Typically, the clinical ERG is elicited by full-field (Ganzfeld) flashes of light. With an appropriate selection of test and background lights, rod and cone function can be assessed separately (1). As the ganglion cells contribute relatively little to the full-field flash ERG, the ERG has helped neuro-ophthalmologists to distinguish between diseases of the outer retina (affecting photoreceptors and/or bipolar cells) and diseases of the inner retina (ganglion cells) and optic nerve. However, because the ERG is the sum of all retinal activity, relatively large retinal defects may not be detected by standard full-field ERG testing. Although the pattern ERG and focal ERG can both provide information about visual loss from lesions in the foveal region (2,3), these techniques do not provide topographical information or assessment of nonfoveal lesions.

The multifocal ERG (mfERG) technique was developed by Sutter et al. (4-6) to provide a topographical measure of retinal activity. With the multifocal technique, 61 or 103 focal ERG responses can be recorded from the cone-driven retina within minutes. Although the technique is relatively new, hundreds of centers around the world have the equipment necessary to record mfERG responses. The equipment developed by Sutter (Electro-Diagnostic Imaging [EDI], San Mateo, CA) dominates the market, but equipment from other companies (such as Roland Instruments, Germany) can be found outside the United States.

The mfERG has been used widely to diagnose and study retinal diseases (7). In fact, over 200 articles on the mfERG, most dealing with clinical topics, have been published within the past 5 years. In this review, we discuss the mfERG technique and its applications in neuro-ophthalmology. When combined with automated perimetry, the mfERG is a valuable tool for localization and differential diagnosis.

RECORDING mfERG RESPONSES

The Display

Figure 1A,B shows the mfERG display used in the work summarized here. Similar to the display originally described by Sutter and Tran (5), it is a standard part of the VERIS software (EDI, San Mateo, CA) developed by Sutter (4-6,8). It consists of 103-scaled hexagons that subtend approximately 50° in diameter when viewed at 32 cm. The scaling of the hexagons is selected to produce approximately equal-sized mfERG responses from individuals with normal retinal function (5). In Figure 1A, the width of the central sector is about 3°, whereas the width of the outermost sector exceeds 7°. For clinical purposes, some investigators have used a display of 61 hexagons, which produces larger responses but has poorer spatial resolution.

A wide range of stimulus intensities has been used. However, the International Society for Clinical Electrophysiology in Vision (ISCEV) guidelines for the mfERG...
FIGURE 1. The multifocal electroretinogram (mfERG) display. A, Top: The mfERG display with circles drawn to indicate radii of 5° (thick dark gray), 15° (thin black) and 25° (dashed light gray). Middle: A schematic of the eye to illustrate where the image of the display falls. Bottom: The 3D mfERG density plot of the responses (E) from a normal subject’s OD. B, The mfERG display at one moment in time. C, The stimulation sequence of 2 sectors in (B). D, The single continuous ERG record generated by the display. E, The 103 mfERG responses (first-order kernel) extracted by correlating the stimulus sequence (C) with the continuous ERG record (D).

(9) suggest that the luminance of the white hexagons be set to a value between 100 and 200 cd/m². For the work described here, the luminance of the white hexagons is 200 cd/m² and the luminance of the black hexagons is about 2 cd/m², the darkest the screen allowed. The luminance of the area surrounding the array of hexagons is set at 100 cd/m² and a central cross is used for fixation. All recordings are performed with the room lights on to help assure a constant state of light adaptation. Because of the light levels used and the rapid rate of stimulation, the mfERG is a response of the cone system.

Recording the Signal
In general, the mfERG signal is recorded with the same electrodes and amplifiers used for conventional ERG recording. The critical differences are the display, the method of stimulation, and the analysis of the raw records. For the records shown here, a single continuous ERG record is obtained with a Burian-Allen contact lens electrode, although a variety of electrode types can be used. The most commonly used noncontact lens electrode is the DTL (10). The contact lens electrode is less comfortable to wear but yields superior records. Although it is possible to analyze records offline (11–13), all the analyses shown here are done with the VERIS software that is part of the system from EDI.

From a single, continuous ERG signal (Fig. 1D), the software extracts 103 mfERG responses, each associated with one of the sectors of the display (Fig. 1E). That is, 103 responses are obtained from a single record. To get a sense of how this is possible, the nature of the local stimulation of each sector must be examined.

Stimulation and Extraction of the Local Responses
To understand the mfERG technique, it is essential to understand how each of the sectors is varied during the test. Each sector is an independent stimulus. Every 13.3 milliseconds, the frame of the monitor changes and each sector has a 50% chance of appearing “white” (briefly flashed) or “black” (no flash). Figure 1C shows a series of frame changes for 2 of the locations. Each of the 103 sectors of the display in Figure 1A,B goes through its own pseudorandom sequence. In fact, the 103 pseudorandom sequences are the same series of “white” or “black” presentations, but the sequence for each of the hexagons starts at a different point in the series. The rationale for this technique is complicated (4–8); it is sufficient to know that these pseudorandom sequences allow the software to rapidly extract the response associated with each of the 103 hexagons.

Figure 2A provides a non-technical explanation of how it is possible to extract 103 responses from a single record. Were one to sum the first 60 milliseconds of the records following the frames during which a particular hexagon appeared white, the response would look like R in Figure 2A. Likewise, were one to sum the first 60 milliseconds of the records following the frames during which the same hexagon appeared black, the response would look something like NR in Figure 2A. Response R contains the responses to all the hexagons that flashed (appeared white), including the hexagon in question. Response NR, on the other hand, contains the responses to all the hexagons except the hexagon in question. The difference between R and NR is the response to the hexagon in question. These responses (Fig. 1E) are called first-order kernels. (For a more realistic picture of the waveforms underlying the first-order kernel, see Fig. 2B in reference 7.) Although the software could, in principle, calculate the 103 mfERG kernels or responses in this way, it does not. Technically, each mfERG response (Fig. 1E) is the result of a serial correlation between the stimulation sequence of a particular hexagon...
The pseudorandom sequence (an m-sequence) is chosen such that, when coupled with a special algorithm, the software can make these calculations very quickly (4). Because of the patent held by EDI on the m-sequence, other manufacturers use different methods of extracting the multifocal responses.

Displaying the Responses

Figure 1E shows the 103 mfERG responses for stimulation of the OD of a control subject. These responses are positioned so that they do not overlap and thus the scaling is arbitrary, as a comparison of the circles in Figures 1A and 1E indicates. We find the trace array in Figure 1E to be the most useful presentation of the data. In some cases, it is helpful to sum or average the responses within various regions of the display. Often responses are summed within rings around fixation. In Figure 3B, the responses from Figure 1E are grouped by rings around fixation (Fig. 3A) and summed. The responses become larger with increased eccentricity from the fovea because progressively larger areas of the retina are being summed. To take area into consideration, the amplitude of the summed response is divided by the total area of the hexagons in that ring. The resulting responses (Fig. 3C) are expressed in a measure of response amplitude per unit area or response density (nV/deg²). As expected, the response per unit area is highest in the fovea (5).

Although this analysis by rings is useful for many purposes, it is not an appropriate display for summarizing the effects of retinal diseases that have nasotemporal asymmetries. It also obscures the nasotemporal differences that are present in the normal mfERG (7,13). However, the software available to analyze the mfERG allows for the combination of responses from any arbitrary grouping of hexagons (Figs. 8–10).

The mfERG results are often displayed in a 3D plot. Figure 1A (bottom) shows the results from Figure 1E as a 3D plot. To obtain this display, the response amplitude is divided by the area of the hexagon (the response density is obtained for each hexagon). In the control subject, there is a depression and a peak associated with the optic disc and the fovea, respectively. Although the 3D plot is pleasing to the eye, it can be very misleading (see below). The 3D plot

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.
should never be analyzed, or published, without the associated trace array.

**Normative Values and Reproducibility**

Several investigators have published normative values for the mfERG (14–17). As expected from full-field ERG studies, the amplitude decreases and the implicit time increases with decreasing luminance. However, as is the case for all electrophysiological tests, it is important that each clinic establish its own age-related norms. The intra-individual reproducibility of the mfERG is good (18). In fact, one group reports it is better than that of static automated perimetry (19).

**THE ORIGIN OF THE mfERG SIGNAL**

As typically recorded, the mfERG signal originates from the central 25° (radius) of the retina (Fig. 1A). The display covers only about 25% of the cone photoreceptor cells (20). Furthermore, the high rate of stimulation, combined with the light levels used, assures that the rods do not contribute except under very unusual circumstances (21,22). Like the traditional photopic, or cone-driven, ERG, the mfERG shows an initial negative component (N1) followed by a positive component (P1) (Fig. 3C). These components bear a superficial resemblance to the a- and b-waves of the photopic flash ERG. However, the waveform of the mfERG differs from that of the typical photopic ERG (7,20). This is not surprising as both the stimulus and the analysis are different. Recall that the standard, full-field ERG is the sum of one or more responses to single flashes. In contrast, the mfERG is not a response at all, but rather a mathematical extraction (Fig. 2A). Thus, the components of the mfERG should never be referred to as the a-wave and b-wave (9).

In spite of these differences, it appears that N1 comprises the same components as the a-wave of the full-field ERG and P1 comprises the same components as the positive waves (b-wave and oscillatory potentials) (7,20). As in the case of the full-field ERG (23,24), the mfERG waveform is largely shaped by bipolar cell activity, together with small contributions from the photoreceptor cells and inner (amacrine and ganglion) retinal cells (25). Figure 4 displays the model of Hood et al. (25) explaining how the cells of the outer retina contribute to produce the mfERG waveform, shown as the solid black curve. The N1, P1, and N2 components are influenced in different ways by the onset and offset of the bipolar cells and, to a much lesser extent, of the photoreceptors. The inner retina exerts a subtle influence on the waveform. In the monkey, for example, the “ledge” on the trailing edge of P1 is removed by blocking the action potentials from the amacrine and/or ganglion cells (25–27).

Analysis of the components of the mfERG (Fig. 4) reveals an important message. Damage at, or before, the bipolar cells will substantially decrease the amplitude of the mfERG. Inner retinal damage to amacrine and/or ganglion cells does not affect mfERG amplitude, although it may have a small effect on its waveform (26,28–31). As an example, Figure 5 shows the mfERG responses recorded 8 months after the occurrence of ischemic optic neuropathy. The responses have been summed within each quadrant for OU. Although there is extensive ganglion cell damage, as imputed from the Humphrey visual fields (HVF) (upper panels of Fig. 5), the mfERGs from the affected eye are similar to those from the unaffected eye.
CLINICAL APPLICATIONS

Over the past 4 years, we have routinely recorded mfERGs from patients evaluated by two neuro-ophthalmologists, Drs. Myles M. Behrens and Jeffrey G. Odel. The following examples illustrate our experience with the mfERG as a diagnostic tool.

Excluding Outer Retinal Disease

The neuro-ophthalmologist is routinely faced with deciding whether a visual defect is due to damage to the outer retina (before the ganglion cells) or damage to the ganglion cells and/or optic nerve. The mfERG can be very helpful, especially in situations where standard tests provide ambiguous information. Because damage to the ganglion cells or optic nerve does not decrease the amplitude of the mfERG, an abnormal mfERG provides strong evidence for an outer retinal lesion.

Patient 1 is a 16-year-old girl with a 1-year history of difficulty reading, especially with her OS. Her visual acuity was 20/25-2 OD and 20/60-1 OS. A full-field ERG was normal and the diagnosis of optic neuritis was entertained. However, the mfERG (Fig. 6B) clearly suggests an outer retinal lesion, particularly when compared with the visual fields. Iso-degree contours have been added to both the mfERG responses (Fig. 6B) and the 24-2 HVF (Fig. 6A) to aid in this comparison. More sophisticated procedures for comparing the HVF to the mfERG exist (32), but these contours are sufficient for most clinical purposes. The agreement between the depressed amplitude of the mfERG (Fig. 6B) and the regions of the HVF defects (Fig. 6A) confirms that the lesion lies in the outer retina. The mfERG, reduced in amplitude but relatively unchanged in implicit time, resembles that seen in Stargardt’s disease (33).

Patient 2 is a 41-year-old man with a 4-month complaint that the vision in his OS resembled a “smudge” on his glasses. He had no complaints about the vision in his OD. His fundus appeared normal and his visual acuity was 20/20 in both eyes. The 24-2 HVFs (Fig. 7A) showed paracentral ring scotomas OU. Glaucoma and retinopathy were possible diagnoses. As shown in Figure 7B, the diagnosis is not glaucoma, as the mfERG is depressed in regions corresponding to the field defects. He was later shown to have abnormal antibody activity suggestive of melanoma-associated retinopathy.

Patient 3 is a 58-year-old woman who had a 10-year history of episodic flashing in both eyes, most often in the OD, suspected of being migrainous in nature. Several weeks prior to her visit, the flashes seemed different and appeared only in the superior temporal field of the OD, in the region corresponding to the defect seen on her HVF (Fig. 8A). Her fundus appeared normal except for mild irregular narrowing of the branch retinal artery in the region of the defect. The subtle change in the amplitude of the mfERG responses in the region of the defect (Fig. 8B), combined with the narrowed artery, suggested branch retinal artery occlusion (BRAO), a condition known to affect

both the inner and outer (bipolar cells) retina. Localized defects are sometimes easier to visualize in the 3D plot (Fig. 8D) and in the second-order kernel array (Fig. 8C) (34). (See the Appendix for a discussion of the second-order kernel.)

The neuro-ophthalmologist is occasionally faced with a patient with two comorbid ophthalmologic conditions, each of which could, in principle, explain the patient's visual loss. Two examples are worth considering here as they illustrate additional points. Patient 4, a 43-year-old man, was a former Olympic soccer player whose MRI showed a third ventricular tumor adjacent to the anterior visual pathway. A nasal scotoma OD was found on visual field testing (Fig. 9A). Visual acuity was 20/20 OU and his fundus examination OD revealed a region of hyperpigmentation in the temporal retina. A mfERG was obtained to determine whether the tumor or a retinal problem was the cause of the defect. There was a local decrease in the mfERG OD in the region of the scotoma. This is best seen by comparing the responses from the two eyes (Fig. 9B). Since there are nasotemporal variations in the mfERG that can be quite large in some individuals, it is important to compare responses from corresponding regions of the retina. The responses from the OS (black) are left-right reversed in Figure 9B so that nasal and temporal regions are aligned. The mfERG is smaller in the region of the defect. Therefore, the retinal lesion rather than the tumor is the cause of the scotoma.

Patient 5 is a 61-year-old woman with a history of a OS branch retinal vein occlusion (BRVO) occurring 3 years prior to presenting for investigation of a visual field defect in her OS (Fig. 10A). Her visual acuity was slightly reduced in the OS (20/30) and intraocular pressure was normal at 16 mm Hg. There was probable disc excavation in the OS. The mfERG was normal in the region of the visual field defect (see dashed rectangles in Fig. 10). Thus, normal tension glaucoma is the likely cause of this defect. Notice, however, that there is a small decrease in the mfERG amplitudes in the macula corresponding to macular edema secondary to the old BRVO (see black circles in Fig. 10).

Differentiating Among Retinal Diseases

The mfERG can help to differentiate among retinal diseases based on changes in the relative amplitudes and latencies of N1 and P1 (See Table 1 in reference 7 for a review.) A large delay in the timing of the mfERG is associated with damage to the photoreceptors/outer plexiform layer (7). Damage to bipolar, amacrine, or ganglion cells yields relatively small changes in the implicit time of P1 and may even shorten it.

Patient 6, a 62-year-old man, had a long history of difficulty with reading, but only mildly reduced acuity
FIGURE 10. Patient 5: Branch retinal vein occlusion (BRVO) versus glaucoma. The OD 24-2 Humphrey visual fields. The dashed rectangle indicates an inferonasal scotoma OS. The black circle circumscribes the paramacular region OS. B, The OS (black) and OD (gray) multifocal electroretinogram (mfERG) responses. The responses for the OD are flipped about the vertical axis so that for both eyes, the nasal field responses are presented on the right and the temporal field responses on the left. The areas inside the dashed rectangle and black circle indicate spatially equivalent areas to those marked in (A). The sum of the responses for these areas is shown in the inset. The mfERG amplitudes are not reduced in the region corresponding to the visual field defect, indicating that the defect is due to glaucoma and not BRVO.

(20/20 OD; 20/40 OS). His retinal evaluations, including angiograms, were normal. Visual fields showed bilateral central scotomas. The left panel of Figure 11A shows the 24-2 HVF of his OS. Because of the nature of his visual fields and a normal-appearing fundus, he underwent repeated and extensive neuroradiologic, neurosurgical, neurologic, and serological examinations, all normal. The mfERG (Fig. 11A, right panel) showed reduced amplitudes in the central 5°and delayed implicit times at all locations, including those where the Humphrey visual fields were normal. The delays can be seen more easily in Figure 11B, where the first 40 milliseconds of the responses are shown for this patient (right panel) and for a normal subject (left panel). Delays such as these are seen in cone dystrophy (35) and retinitis pigmentosa (36,37) and are associated with damage to the receptors/outer plexiform layer (7). The findings for this patient fit the definition of occult macular dystrophy proposed by Miyake and colleagues (38). Such patients present with normal to moderately reduced visual acuity, normal peripheral fields, small central or paracentral defects, and normal, or only mildly abnormal, full-field ERGs. They are best diagnosed with focal ERGs or mfERGs.

Following Disease Progression

Because the mfERG shows good repeat reliability (18,19), it can be used to follow the progression of a disease. This is particularly helpful in the case of patients who are poor field takers, but it can be of value in other cases as well.

Patient 7 provides an example where following the mfERG changed the diagnosis. The mfERGs in Figure 12B are delayed in all regions of the field except the central region, as is often seen with diseases of the receptors and pigment epithelium such as retinitis pigmentosa (RP) and cone dystrophy (7,35–37). Although we initially thought that the patient's problem was RP, her visual field continued to deteriorate at a rate far too fast for RP. Figure 12C and D show her HVF and mfERG responses obtained 15 months later. The field has become more constricted and the mfERG amplitudes have markedly decreased in the region previously showing the delays. We subsequently found evidence of retinal antibodies, and an autoimmune process is suspected.

Differentiating Organic from Nonorganic Disorders

The mfERG can be used to diagnose nonorganic disorders. The advantage of the mfERG over the conventional ERG is that it provides a topographical representation that can be compared with the patient's visual fields. Patient 8 is
FIGURE 12. Patient 7: Possible immune-mediated outer retinopathy. The baseline OS visual field (A) and multifocal electroretinogram (mfERG) (B). Recorded 15 months later, the OS visual field (C) and mfERG (D) show substantial progression. Arrows point to geographically equivalent areas.

A 30-year-old policeman who had complained of decreased vision in his OS for the past few years, especially during the day. A nonorganic disorder was in the differential diagnosis. However, the mfERG shows depressed responses in the macula (Fig. 13, right panel). This prompted indocyanine green angiography and optical coherence tomography, which suggested a resolved central serous chorioretinopathy. A normal mfERG does not, by itself, establish a visual deficit as nonorganic. If the mfERG is normal, then a multifocal VEP should be performed as well to rule out damage to the optic nerve/ganglion cells.

FIGURE 13. Patient 8: Resolved central serous retinopathy in suspected nonorganic visual loss. Visual field (left) and multifocal electroretinogram (mfERG) (right). Reduced foveal mfERG amplitudes suggested that the depressed foveal thresholds had a retinal origin, which prompted indocyanine green angiography and optical coherence tomography that suggested that resolved central serous retinopathy is the cause of visual loss.

A. Normal B. P9


SOME LIMITATIONS

Eccentric Fixation

As in the case of visual field testing, it is important to monitor the patient’s eye position. An eye camera or direct visualization of the eye should be used to assure that fixation is steady. Unsteady fixation can cause diminished responses in the center of the field. Monitoring the eye, however, will not assure that the fixation is accurate. Some patients with central visual problems can have eccentric fixation, which will produce mfERGs that appear to have central and paracentral defects. Figure 14, which illustrates this point, contains the mfERG from a normal individual who was instructed to fixate down and to the left by 8.5° from the center (Fig 14C). Notice the smaller responses in the central part of the field. These are due to the fact that with eccentric fixation, the small central hexagons are now falling outside the fovea. Eccentric fixation can be detected...
by the pattern of results in both the trace array (Fig. 14C) and 3D plot (Fig. 14E). Since the fovea is now stimulated by larger hexagons, the responses in the region of fixation will be abnormally large. In the 3D plot, the blind spot also has been shifted (Fig. 14E). The latencies of the mERG responses can also be used to identify the foveal and blind spot regions (see ref. 13 and Fig. 13 in ref. 7). The mERG from Patient 9 provides a clinical illustration of eccentric fixation. Patient 9 is a 64-year-old woman with psoriatic arthritis who had been treated with both hydroxychloroquine and infliximab. She complained of a loss of vision in her OD, and her visual field demonstrated a marked generalized depression (Fig. 14B). Her mERG showed a decrease in response amplitude in the central 5° or so (Fig. 14D). However, her field depression extended at least to 25° (Fig. 14B). Before one can conclude that the retina is the site of the damage, eccentric fixation must be ruled out.

The patient's visual acuity was 20/400 OD and she could not see the fixation target. Her fixation was monitored during the test and it was steady. However, her mERG (Fig. 14D, F) indicates that she is clearly fixating off center. The pattern of her mERG resembles that in Fig. 14C, E. The location of the foveal peak and optic disc depression are both consistent with fixation up and to the left of the fixation target. Thus, her retinal function appears grossly normal and the damage must be at or beyond the ganglion cells. The message is clear: if care is not taken in the recording and interpretation of mERGs, depressed central responses due to fixation errors can be misinterpreted as a retinal problem.

The 3D Plot Can Be Misleading

The 3D plot can be misleading and should never be presented without the associated trace array. Consider the records in Figure 15A. These responses were obtained from an electrode in saline. There are no responses here, only noise. However, since the 3D plot (Fig. 15B) is obtained by dividing the response (which, in this case, is the same everywhere) by the area of the local hexagon (which is smaller for the central hexagons), a "foveal peak" is present. Figure 15C–F provides a clinical example of where the 3D plot was misleading. Patient 10, a 66-year-old woman with multifocal choroiditis and panuveitis, had a visual acuity of counting fingers in her OD. Her OD mERG was performed in June 2000 (Fig. 15C, E) and again 18 months later (Fig. 15D, F) to see if any recovery had taken place. The 3D plot in Figure 15D suggested an improvement. However, as her trace arrays and ring averages (Figs. 15E-H) indicate, there is little or no response on either day. The noisier records on the second day produced the artifactual peak at the fovea.

Although 3D plots can be useful for visualizing small scotomas (Fig. 8B) and the blind spot (Fig. 14E, F), they...
should be used sparingly, and always in conjunction with the trace arrays.

The Spatial Resolution of the mfERG

Since the mfERG is a topographical map of retinal function, it is important to know its spatial resolution. Spatial resolution will be influenced by a variety of factors, including the degree of light scatter in the eye, the size of the hexagons in the test display, and the stability of fixation. A systematic consideration of these factors has yet to be published. In our experience, scotomas at least as small as 4° can be detected (see Figs. 8 and 9 and Fig. 7 in ref. 7).

CONCLUSIONS

The mfERG has become a useful test to detect regional outer retinal disorders that are not sufficiently extensive to significantly reduce the full-field ERG. However, to optimize its value, it is important to compare mfERG results to those of automated visual fields obtained concurrently. Seeing abnormal mfERGs in the same regions of the visual field that are abnormal on automatic perimetry provides a high degree of reassurance of the retinal origin of the defect.

Recording mfERGs requires skill and experience. The challenges in recording and analyzing mfERG responses are greater than those involved in full-field ERG testing. Even so, those who are already recording high-quality ERGs should be able to master the skill. mfERG testing is otherwise best left to centers with an electrophysiologist familiar with the technique.

APPENDIX

The Second-Order Kernel

It is important to have some understanding of the second-order kernel or response (2K), because some investigators have claimed diseases of the ganglion cell/optic nerve affect it differentially. Like all the multifocal responses, it is not technically a “response” but a mathematical extraction. Figure 2B provides a simple way to understand the meaning of the 2K. The flashes in Figure 2A that make up the first-order response (1K) can be divided into two groups. Half of the times that a particular hexagon appeared white, a flash preceded it (small white hexagon in Fig. 2B). On the other half of the times, a flash did not precede it (small black hexagon in Fig. 2B). If the responses under the two conditions are the same, then there is no 2K. If these two responses differ, then there is a 2K and it is the difference between the 1K responses. Thus, the presence of a 2K indicates that there is an effect of short-term adaptation. In the normal mfERG, the presence of the flash on the preceding frame makes the response slightly smaller and slightly faster. Thus, the shape of the 2K is complex as indicated in Figure 2B.

Some investigators speak as if the 2K is an actual response generated in the inner retina. Some even claim that it is generated by the ganglion cells. As the discussion above indicates, the 2K is not a response and thus strictly speaking cannot be generated anywhere. We do know that blocking action potentials generated by the ganglion cells and amacrine cells in monkeys markedly reduces, but does not eliminate, the 2K (25). On the other hand, although ganglion cell damage can reduce the 2K in humans (28), a large 2K can be present even with extensive damage (29). Therefore, it appears that inner retinal damage, but not necessarily ganglion cell damage, can decrease the 2K in humans. However, outer plexiform damage can completely eliminate the 2K in patients with degenerative diseases of the receptors (7). Consequently, it is a mistake to associate a diminished 2K with damage to a particular set of cells. A diminished 2K indicates an abnormality in the circuits and connections involved in adaptation rather than a missing component or cellular response (7).

The 2K can be useful, however, in identifying local lesions of the inner nuclear layer and/or receptors. As mentioned above, the 2K is reduced more than the 1K by BRAO (34), as can be seen in Figure 8. Although the selective loss of the 2K has been interpreted as an indication of inner retinal damage (34), it can be caused by damage at the outer plexiform layer as well (7). Furthermore, it is likely that the relatively larger loss of the 2K response as compared with the 1K in BRAO is due to a reduced effect of stray light (7,39). For example, Shimada and Horiguchi (39) have shown that the spatial resolution of the 2K is better than the 1K because the 2K has a smaller contribution from stray light.

Other Paradigms

The software available for creating displays and for modulating the temporal sequence of light presentations allows for a wide range of spatial and temporal paradigms. A number of paradigms have been developed to help detect damage to the inner retina (i.e., amacrine and ganglion cells) (e.g., [40–45]). The best developed of these is the global flash paradigm (40). This paradigm is designed to accentuate a component generated at the optic nerve head (ONH) by action potentials from ganglion cells. The existence of an ONH component has been fairly well established (27,28), and there is some evidence that glaucoma can eliminate it (40). However, the ONH component is small and its usefulness in detecting glaucomatous damage is uncertain (45). Until more evidence is presented, we do not recommend using the mfERG to study diseases of the ganglion cell/optic nerve. If an electrophysiological measure of ganglion cell/optic nerve is needed, the multifocal VEP is a better candidate (46).
Acknowledgments
The authors gratefully acknowledge the support and encouragement of Myles M. Behrens, MD.

REFERENCES
The 127th annual meeting of the American Neurological Association was held in New York City from October 13 to 16, 2002. I attended the half-day plenary session consisting of nine oral presentations on October 15th and report my observations. Publications of the presentations are referenced.

Leading off the session was an oral presentation on the use of gene therapy to reverse the mitochondrial deficiency of Leber Hereditary Optic Neuropathy (LHON) in cultured cells. The authors used a recombinant adenovirus (AAV) as a vector to deliver a normal ND4 subunit gene of complex I to hybrid cells containing the G11778A mutation in mitochondrial DNA in a neutral nuclear background. The G11778A mutation in mitochondrial DNA is responsible for approximately half of all LHON cases.

The AAV-delivered ND4 subunit gene was specially constructed for expression in the nucleus. Because of the partially different genetic codes between the nucleus and mitochondria, a mitochondrial gene encoding a normal ND4 subunit gene could not be used for gene expression outside the mitochondria.

To import the normal ND4 protein, generated by the nuclear encoded ND4 gene from the cytoplasm into the mitochondria, a mitochondrial targeting sequence was added to the beginning of the gene. Next, to visualize the ND4 imported into mitochondria, a short FLAG epitope tag was added to the end of the nuclear-encoded ND4 gene. The FLAG-labeled ND4 was then detected with an antibody against the FLAG. Cells infected with AAV containing this ND4FLAG gene had restored to normal levels the 60% decrease in ATP synthesis found in these hybrid LHON cells, even in the presence of the mutated mitochondrial DNA (1).

The technology to deliver DNA directly to mitochondria still does not exist. The allotopically expressed ND4 is the next best alternative for the treatment of LHON. In fact, 85% of all mitochondrial proteins are expressed in this fashion. Perhaps to address the issue with LHON, parallel studies can be conducted using the model system of Leonard Levin, MD; axotomized retinal ganglion cells (4) without axotomy. By using the complex I inhibitor rotenone as the neurotoxin, one could then test whether optic nerve axons or retinal ganglion cells are the targets of experimentally induced mitochondrial deficiency.

The third oral presentation dealt with the mechanisms of progression of single seizures to status epilepticus. Wasterlain et al showed a five-fold increase in NMDA receptors 40 to 70 minutes after experimentally induced seizures (5). This resulted in status epilepticus that was refractory to standard anticonvulsants, but was quickly abolished by the use of NMDA antagonists such as ketamine. These results suggest a new treatment avenue for refractory seizures and status epilepticus (6).

The fourth oral presentation elegantly used magnetic resonance imaging (MRI) and positron-emission tomography (PET) to study the role of suicide gene therapy in eight patients with glioblastoma multiforme. The authors, all from Germany, introduced the herpes simple virus gene thymidine kinase directly into the tumor by continuous infusion, then performed PET after injection of the tracer $^{[124I]}$ 2'-fluoro-2'deoxy-1-B-D-arabinofuranosyl-5-iodouracil (FIAU) as a specific marker substrate for herpes simplex virus thymidine kinase. To kill the tumor cells expressing herpes thymidine kinase, they began treatment with ganciclovir 4 days after infusion of this suicide gene. In only one of eight patients did they find colocalization of FIAU (the marker of herpes thymidine kinase gene
expression) to the areas of tumor necrosis imaged by PET as showing decreased tumor uptake of \(^{18}F\) fluorodeoxyglucose or \(^{11}C\) methionine. While the gene expression was not seen in the entire tumor bed, I believe this patient had the longest survival (8 or 9 months).

Although the neuroimaging was striking, the gene therapy did not appear to substantially increase patient survival (7–9). However, the series was small and each of the patients enrolled in this open-ended study had already failed the standard treatments for glioblastoma multiforme. Because gene therapy is not 100% efficient (it more closely approximates 50%), perhaps this form of treatment would have been more effective had it been done more than once, even though the authors used an infusion rather than simply an injection of the suicide gene. Perhaps repeated cycles of infusion of the gene, followed by ganciclovir administration, will be needed to completely eradicate the tumor.

The seventh oral presentation studied the defects of coenzyme Q10 in slowing the functional decline associated with early Parkinson disease. Shults et al (10) randomly assigned patients to receive either placebo or oral treatment with coenzyme Q10 at 300 mg, 600 mg or 1200 mg/day for 16 months. They found a clinically significant treatment effect that was greatest at the higher doses.

Although Parkinson disease is not caused by mutated mitochondrial DNA (11), complex I activity is markedly reduced in this disorder (12). The higher doses of coenzyme Q10 used in this study of Parkinson disease may also be applicable to the treatment of other disorders with complex I dysfunction, such as LHON and MELAS (13). Probably all of us have already tried much lower doses of coenzyme Q10 (the standard 25 mg capsule) without effect in our LHON patients. The results of this study in Parkinson disease suggest that maybe we should be using high doses of coenzyme Q10 in treating LHON.

Among over 300 poster presentations, here are the highlights:

In poster No. 30, Ikeda et al (14) from Japan used a novel neuroprotective compound T-588 to rescue motor neurons of the facial nerve after nerve avulsion. Rats treated orally with his compound for 1 to 4 weeks after facial nerve avulsion had less histopathologic degeneration and better motor neuron function than did placebo-treated rats. The authors have already shown this compound to be effective in a mouse model of motor neuron degeneration, but perhaps this could be applied to some patients with facial nerve paralysis after neurosurgery for large acoustic neuromas. Alternately, most neuroprotective agents have failed miserably in clinical trials (15–17).

Poster No. 45 studied the role of alcohol in dementia. Truslen et al (18) from Denmark found that beer was associated with an increased risk of dementia, and wine with a decreased risk; spirits had no effect on risk. Perhaps we should all be switching to a good wine.

In poster No. 88, Toosy et al (19) used photic stimulated functional MRI to study cortical activation in eight patients who had recovered from optic neuritis. All subjects had normal visual acuity and color vision. They found that whereas visual cortex activation was reduced, extra-occipital activation was increased. They concluded that this “adaptive reorganization” may contribute to the visual recovery classically attributed to remyelination of the optic nerve.

This work seems to support Sabel’s (20) hypothesis that brain plasticity can provide the substrate for restoration of vision. His work claims to show that visual field defects caused by irreversible optic neuropathy can be improved by using repetitive cortical stimulation of partially damaged areas with daily computer-based visual restitution training. He claimed that enlargements in the visual field were significant and that they were maintained after the training was stopped.
Poster No. 90 examined mtDNA mutations in Devic disease. Although Kalman et al (21) detected several homoplasmic variants, these were felt to represent polymorphisms that were also present in their control populations with and without multiple sclerosis (MS). However, the authors did find a common genetic background, a shared haplotype between some patients with MS and Devic disease.

Poster No. 93 tested a new avenue for MS treatment based on the EAE animal model. Using an antibody against macrophage migration inhibition factor (MIF), Ogata et al (22) reduced the severity of EAE. They also found higher levels of MIF in active lesions of MS brains obtained at autopsy.

Macrophages are the effector cells in both MS and EAE. These phagocytic cells strip and ingest myelin. Blocking the effects of MIF may add significantly to MS treatment. The recent approval of natalizumab (Antegren®) (23,24) to block inflammatory cell migration across the blood-brain barrier may also have comparable impact. However, the side effects of infection may turn out to be less with MIF as it only affects leukocytes associated with chronic disease—macrophages rather than polymorphonuclear leukocytes. Natalizumab affects migration of both kinds of white blood cells.

Poster No. 97 described a new antiinflammatory peptide, RDP 58, as a potential therapy for multiple sclerosis. RDP58 is a 10-amino acid peptide with multiple antiinflammatory activities (25,26). It inhibits proinflammatory cytokines such as tumor necrosis factor and interferon-γ, while at the same time upregulating defenses (heme oxygenase-1) against immune mediators. RDP58 reduced EAE disease activity best when given 10 days after antigen sensitization.

While this appears promising for the treatment of MS, a major drawback is that the peptide was given by intracerebral ventricular injection. In addition, tumour necrosis factor inhibitors actually increased MS disease activity when tested in clinical trials (27), though they suppressed EAE (28).

In poster No. 146, Mastromardi et al (29) found that adding vitamin B₁₂ supplementation (15 mg/kg) to interferon therapy had a greater suppressive effect on EAE (70–80%) than using interferon (30%) or vitamin B₁₂ (20%) alone. These results are very encouraging, as combination therapy with copaxone and interferon have not had a synergistic effect, even though the mechanisms of disease suppression are different for each agent.

Poster No. 210 examined the role of molecular mimicry as a cause of neurologic diseases. Molecular mimicry is characterized by an immune response to an exogenous agent that cross-reacts with a host antigen such that the resultant autoimmune reaction causes disease. Of ten patients who developed neurologic impairment after vaccination for Lyme disease, four had homology between the Lyme outer surface protein A (OSP A) and human neural tissue. In addition, HTLV-1 patients also developed antibodies to neurons. The human heterogeneous nuclear ribonucleoprotein-A1 (hnRNP-A1) was found to be cross-reactive with the human T-lymphotropic virus type 1 associated with myelopathy/tropical spastic paraparesis, a disease that can be indistinguishable from MS.

Although deletion of the cross-reactive sequences from future vaccines might prevent the neurologic complications associated with Lyme vaccination, the search for the agent responsible for molecular mimicry in multiple sclerosis continues. Herpes virus is considered a prime candidate (30).

In poster No. 211, intravenous immunoglobulin therapy (25–30 mg/kg/d for 4 days) was used to treat two patients with Susac Syndrome who did not respond to high-dose corticosteroids. They found a transient improvement in the encephalopathy.

**REFERENCES**

Oculomotor Ophthalmoplegic Migraine: What Really Causes It?

To the Editor:

In his Hoyt Lecture on oculomotor ophthalmoplegic migraine (OM), Carlow (1) asked the question ‘Is it really migraine?’ As an alternative, could occult vascular malformation within the third nerve be a mechanism for OM?

Oculomotor cavernous angioma has been reported in patients with third nerve palsy and enhancement of the nerve on cranial magnetic resonance imaging (MRI) (2,3). In addition, occult cavernous angiomas in the optic chiasm have been reported to produce acute episodes of visual loss and pain (“chiasmal apoplexy”) with spontaneous exacerbation and remission (4,5). Thus, I have two questions:

1) In Dr. Carlow’s review of the literature, did he encounter any ante-mortem or post-mortem examinations of the oculomotor nerve in a patient with OM?

2) Has there ever been any evidence of hemorrhage using routine MRI or gradient echo imaging in any of these cases or would the lesion be too small to detect blood or an occult vascular malformation within the nerve?

Andrew G. Lee, MD
Department of Ophthalmology
University of Iowa
Iowa City, Iowa
andrew-lee@uiowa.edu

References


Reply:

I would like to thank Dr. Lee for asking two salient and extremely relevant questions regarding ophthalmoplegic migraine (OM). I will address each in order.

1) In Dr. Carlow’s review of the literature did he encounter any ante-mortem or post-mortem examinations of the oculomotor nerve in a patient with OM?

Excluding aneurysm, tumor, brainstem herniation and other explainable causes, only five cases of OM have been autopsied that fulfill the generally accepted clinical criteria for OM.

Weiss (1) reported a case of a 30-year-old woman with repeated episodes of oculomotor paralysis from childhood, who died of tuberculous meningitis in 1885. Gray, warty granulations in the involved third nerve root and at the base of the brain, from which tubercle bacilli were recovered, making this case unhelpful in the quest to understand the pathogenesis of OM.

A second pathologic case was documented in 1887 by Richter (2). A 36-year-old man had a history of recurrent headache and oculomotor paralysis from age 5 years. The involved oculomotor nerve was twice the size of the normal nerve and club-shaped as it passed through the dura. The oculomotor nerve fascicles were separated by connective tissue without nerve fiber degeneration. This thickening was diagnosed as a fibrochondroma; however, there was no documentation of cartilage in the lesion.

Karpus (3) described the third autopsied case of OM. A 43-year-old woman had repeated episodes of headache and oculomotor paresis from age 6 months that ultimately developed into a complete third nerve paralysis. She contracted syphilis at age 18 years and died of periencephalitis chronicus, although the meninges were not included in the histopathologic report. A 6 mm thickened oculomotor nerve at the midbrain exit was diagnosed as a neurofibroma with separation and considerable degeneration of the oculomotor nerve fibers.

In 1911, Shionoya (4) reported a case of a 16-year-old boy who died of acute tuberculous meningitis following repeated attacks of headache and oculomotor paralysis dating from age 6 years. The involved third nerve was five times normal size at the nerve root midbrain exit and was surrounded by purulent exudate. Significant strands of connective tissue were intertwined within the oculomotor nerve fascicles, a finding inconsistent with the histopathology of acute tuberculous meningitis.

In 1951, Alpers (5) documented a 23-year-old woman who had had repeated episodes of headache, ptosis, and diplopia for 1 year. Her last admission was prompted by headache, ptosis, and mydriasis without evidence of ophthalmoplegia. A craniotomy was performed and the third cranial nerve on the involved side was observed at surgery to be normal. A microscopic study of the brainstem revealed no abnormalities. The authors concluded that the third nerve was normal. The histopathology of the peripheral oculomotor nerve, especially at the midbrain third nerve root exit, was not included in the report, which allows their conclusion to be questioned.

The histopathology described in three of the above five cases (2–4) could be consistent with oculomotor nerve...
hypertrophy and scar formation from repeated episodes of demyelination and remyelination and therefore fit with my hypothesis for OM. None of the reports included histopathologic photographs or a detailed microscopic analysis of the involved oculomotor nerve, which will probably be required before the pathophysiology of OM is fully understood.

2) Has there ever been any evidence of hemorrhage using routine MRI or gradient echo imaging in any of these cases or would the lesion be too small to detect blood or an occult vascular malformation within the nerve?

Dr. Lee also wonders whether OM may be associated with a third nerve cavernous angioma. Only four pathologically verified cases of oculomotor cavernous angioma have been reported, two with Robert’s syndrome (6–9). Three had only one episode of oculomotor palsy prior to surgery, and one had no history of ophthalmoplegia. None fulfilled the clinical criteria for OM and all had relatively large lesions on CT. One case had an MRI (9) with features consistent with a cavernous angioma.

No case in my series, or in the cases from my literature review, had evidence of hemorrhage using routine MRI. Resolution of the third nerve using routine T2-weighted MRI is suboptimal. A thickened oculomotor nerve in OM was documented in only one case from my literature review and in two cases from my series using T2-weighted MRI. Gradient echo is more sensitive than routine spin echo imaging in detecting very small areas of hemosiderin deposition in intracranial lesions (10). However, resolution is far less than with T1-weighted imaging and was not used in any case from my review or in my series.

Our ability to resolve minute oculomotor nerve vascular malformations, hemorrhage, or hemosiderin is currently inadequate. A dedicated oculomotor nerve midbrain surface coil utilizing 3D T2-weighted fast spin echo imaging or T2-imaging at high field strength (3.0 Tesla) could potentially improve third nerve resolution enough to resolve the problem.

Thomas J. Carlow, MD
Departments of Neurology and Ophthalmology
University of New Mexico
Albuquerque, New Mexico
tjcarlow@swcp.com

Acknowledgments
I would like to thank Dr. Mario Kornfeld, professor of Neuropathology at the University of New Mexico, who is fluent in German, for translating and interpreting the German papers referenced.

References
Oculomotor Ophthalmoplegic Migraine: What Really Causes It?

To the Editor:

In his Hoyt Lecture on oculomotor ophthalmoplegic migraine (OM), Carlow (1) asked the question 'Is it really migraine?' As an alternative, could occult vascular malformation within the third nerve be a mechanism for OM? Oculomotor cavernous angioma has been reported in patients with third nerve palsy and enhancement of the nerve on cranial magnetic resonance imaging (MRI) (2,3). In addition, occult cavernous angiomas in the optic chiasm have been reported to produce acute episodes of visual loss and pain ('chiasmal apoplexy') with spontaneous exacerbation and remission (4,5). Thus, I have two questions:

1) In Dr. Carlow's review of the literature, did he encounter any ante-mortem or post-mortem examinations of the oculomotor nerve in a patient with OM?
2) Has there ever been any evidence of hemorrhage using routine MRI or gradient echo imaging in any of these cases or would the lesion be too small to detect blood or an occult vascular malformation within the nerve?

Andrew G. Lee, MD
Department of Ophthalmology
University of Iowa
Iowa City, Iowa
andrew-lee@uiowa.edu

References

Reply:

I would like to thank Dr. Lee for asking two salient and extremely relevant questions regarding ophthalmoplegic migraine (OM). I will address each in order.

1) In Dr. Carlow's review of the literature, did he encounter any ante-mortem or post-mortem examinations of the oculomotor nerve in a patient with OM?

Excluding aneurysm, tumor, brainstem herniation and other explainable causes, only five cases of OM have been autopsied that fulfill the generally accepted clinical criteria for OM.

Weiss (1) reported a case of a 30-year-old woman with repeated episodes of oculomotor paralysis from childhood, who died of tuberculous meningitis in 1885. Gray, warty granulations in the involved third nerve root and at the base of the brain, from which tubercle bacilli were recovered, making this case unhelpful in the quest to understand the pathogenesis of OM.

A second pathologic case was documented in 1887 by Richter (2). A 36-year-old man had a history of recurrent headache and oculomotor paralysis from age 5 years. The involved oculomotor nerve was twice the size of the normal nerve and club-shaped as it passed through the dura. The oculomotor nerve fascicles were separated by connective tissue without nerve fiber degeneration. This thickening was diagnosed as a fibrochondroma; however, there was no documentation of cartilage in the lesion.

Karpus (3) described the third autopsied case of OM. A 43-year-old woman had repeated episodes of headache and oculomotor paresis from age 6 months that ultimately developed into a complete third nerve paralysis. She contracted syphilis at age 18 years and died of periencephalitis chronica, although the meninges were not included in the histopathologic report. A 6 mm thickened oculomotor nerve at the midbrain exit was diagnosed as a neurofibroma with separation and considerable degeneration of the oculomotor nerve fibers.

In 1911, Shionoya (4) reported a case of a 16-year-old boy who died of acute tuberculous meningitis following repeated attacks of headache and oculomotor paresis dating from age 6 years. The involved third nerve was five times normal size at the nerve root midbrain exit and was surrounded by purulent exudate. Significant strands of connective tissue were intertwined within the oculomotor nerve fascicles, a finding inconsistent with the histopathology of acute tuberculous meningitis.

In 1951, Alpers (5) documented a 23-year-old woman who had had repeated episodes of headache, ptosis, and diplopia for 1 year. Her last admission was prompted by headache, ptosis, and mydriasis without evidence of ophthalmoplegia. A craniotomy was performed and the third cranial nerve on the involved side was observed at surgery to be normal. A microscopic study of the brainstem revealed no abnormalities. The authors concluded that the third nerve was normal. The histopathology of the peripheral oculomotor nerve, especially at the midbrain third nerve root exit, was not included in the report, which allows their conclusion to be questioned.

The histopathology described in three of the above five cases (2–4) could be consistent with oculomotor nerve
hypertrophy and scar formation from repeated episodes of demyelination and remyelination and therefore fit with my hypothesis for OM. None of the reports included histopathologic photographs or a detailed microscopic analysis of the involved oculomotor nerve, which will probably be required before the pathophysiology of OM is fully understood.

2) Has there ever been any evidence of hemorrhage using routine MRI or gradient echo imaging in any of these cases or would the lesion be too small to detect blood or an occult vascular malformation within the nerve?

Dr. Lee also wonders whether OM may be associated with a third nerve cavernous angioma. Only four pathologically verified cases of oculomotor cavernous angioma have been reported, two with Robert’s syndrome (6–9). Three had only one episode of oculomotor palsy prior to surgery, and one had no history of ophthalmoplegia. None fulfilled the clinical criteria for OM and all had relatively large lesions on CT. One case had an MRI (9) with features consistent with a cavernous angioma.

No case in my series, or in the cases from my literature review, had evidence of hemorrhage using routine MRI. Resolution of the third nerve using routine T2-weighted MRI is suboptimal. A thickened oculomotor nerve in OM was documented in only one case from my literature review and in two cases from my series using T2-weighted MRI. Gradient echo is more sensitive than routine spin echo imaging in detecting very small areas of hemosiderin deposition in intracranial lesions (10). However, resolution is far less than with T1-weighted imaging and was not used in any case from my review or in my series.

Our ability to resolve minute oculomotor nerve vascular malformations, hemorrhage, or hemosiderin is currently inadequate. A dedicated oculomotor nerve midbrain surface coil utilizing 3D T2-weighted fast spin echo imaging or T2-imaging at high field strength (3.0 Tesla) could potentially improve third nerve resolution enough to resolve the problem.

Thomas J. Carlow, MD
Departments of Neurology and Ophthalmology
University of New Mexico
Albuquerque, New Mexico
tjcarlow@swcp.com

Acknowledgments
I would like to thank Dr. Mario Kornfeld, professor of Neuropathology at the University of New Mexico, who is fluent in German, for translating and interpreting the German papers referenced.

References

The second combined NANOS/Walsh meeting was enjoyed by 297 attendees at Snowbird, Utah, February 8–13, 2003, bringing to 35 the number of annual Frank Walsh Society Meetings and to 29 the number of NANOS meetings.

The Walsh meeting, organized by a team from the Mayo Clinic, including Jacqueline Leavitt, MD (Rochester, MN) and Brian Younge, MD (Rochester, MN), brought the considerable talents of Mayo neuropathologist Caterina Giannini, MD and neuroradiologist Glenn Forbes, MD to bear on the usual bumper crop of 20 interesting and unusual cases, with runaway discussion held in check at times by moderators Patricia McNussen, MD (Urbana, IL), Misha Pless, MD (Pittsburgh, PA), Pamela Chavis, MD (Richmond, VA), Nick Hogan, MD, PhD (Dallas, TX), Susan Benes, MD (Columbus, OH), Wayne Cornblath, MD (Ann Arbor, MI), Kimberly Peele Cockerham, MD (Pittsburgh, PA), and Lyn Sedwick, MD (Orlando, FL).

After a warm-up with the Walsh session, the NANOS part of the meeting started with a neuro-oncology symposium including invited guest speaker Lisa DeAngelis, MD (New York, NY). That afternoon, there was the first of two practical sessions on office management and insurance issues called “Skip’s Tips” by Skip Legge, MD (Omaha, NE).

In the evening, there were 78 posters to peruse with brew in hand.

The following day featured platform presentations and a controversies session on functional visual loss, which included attorney Dave Williams (Salt Lake City, UT) and psychiatrist Noel Gardner (Salt Lake City, UT), a session on clinical research strategies by Terry Cox, MD (Bethesda, MD), a biostatistics wet lab with Laura Balcer, MD (Philadelphia, PA), and a skills transfer course on the digital office taught by Preston Calvert, MD (Alexandria, VA), Jade Schiffman, MD (Houston, TX), Rosa Tang, MD (Houston, TX), and Edmond FitzGibbon, MD (Bethesda, MD).

Day three brought more platform presentations, which included a fascinating videography on nystagmus in dogs treated with gene therapy by Louis Dell’Osso, PhD (Cleveland, OH). On day four, we were privileged to have a session on multifocal electoretinography and visual evoked potentials directed by Donald Hood, PhD (New York, NY) and an explanation by Lee Jampol, MD.
Dr. Brodsky also announced the new NANOS fellows: Sean Donahue, MD, PhD (Nashville, TN), Todd Goodglick, MD (Chevy Chase, MD), Aki Kawasaki, MD (Lausanne, Switzerland), and Anat Kesler, MD (Petach-Tikva, Israel).

New senior NANOS members include Robert Bedrossian, MD (Vancouver, WA), Ronald Burde, MD (Bronx, NY), David Singer, MD (Aspen, CO), Kenneth Stover, DO (Rancho Santa Fe, CA) and Jonathan Wirtschafter, MD (Minneapolis, MN).

The Young Investigator Award this year was given to Agnes Ming-Fong Wong, MD, PhD, (Tokyo, ON) for her work with congenital strabismus and the effect of early correction on brain pathways. She and her co-workers simulated strabismus in infant macaques with prism goggles, and then studied the different visual outcomes when the goggles were removed at age three weeks (equivalent human age of three months) versus age 3-6 months (equivalent human age, 12 to 24 months). They found that monkeys with reversal of induced strabismus early had considerably better outcomes as assessed by horizontal smooth pursuit, fixation stability, and large field optokinetic movements.
which correlated with abnormalities in the later-corrected macaques in layers 2-4 of the striate cortex.

Born in Hong Kong, Dr. Wong came to Boston University for her undergraduate work, and graduated from medical school at McGill University. She did her ophthalmology residency at the University of Toronto and a fellowship in neuro-ophthalmology with James Sharpe, MD (Toronto, ON) at the same institution, followed by a fellowship in pediatric ophthalmology at Washington University, St. Louis, MO. She did simultaneous work toward a PhD in neuroscience at the University of Toronto, with a thesis titled "Three Dimensional Disorders of Gaze and Binocular Alignment after Brainstem and Ocular Motor Nerve Lesions," under the guidance of Dr. Sharpe and Douglas Tweed, MD, PhD, together with postdoctoral work in collaboration with Lawrence Tychsen, MD, Department of Ophthalmology and Visual Sciences, Washington University, and Andreas Burkhalter, PhD, associate professor of anatomy and neurobiology, Washington University. Dr. Wong, who welcomed her first child, James, on June 7, 2003, is assistant professor of ophthalmology and neurology at the University of Toronto and adjunct assistant professor of ophthalmology, Washington University.

This year's Best Presentation by a Resident/Fellow award went to Nitza Goldenberg-Cohen, MD (Baltimore, MD), who is currently a pediatric ophthalmology fellow at the Wilmer Institute of Johns Hopkins University. Born and raised in Israel, she received her medical degree, master's degree in health administration, and ophthalmology residency training at Sackler Medical School, Tel-Aviv University. In 2001, she came to Wilmer for a fellowship in neuro-ophthalmology under the direction of Neil Miller, MD, and sponsored in part by the Krieger Fund. Her research, which has been guided by Steven Bernstein, MD, PhD, associate professor of ophthalmology, neurobiology, and genetics, University of Maryland, has focused on an elegant mouse model for anterior ischemic optic neuropathy, using photoembolization with a photosensitive dye to selectively target capillaries that serve the anterior optic nerve and spare the retinal blood supply. Her neuropathologic findings suggest that early damage to oligodendrocytes may lead to retinal ganglion cell loss. Dr. Goldenberg-Cohen, her husband, and their three children have enjoyed their sojourn in the United States but planned to return this summer to Petah-Tikva, Israel, where she hopes to continue her research and apply her clinical skills at Schneider Children's Medical Center, Tel Aviv University.

Lyn A. Sedwick, MD
Orlando, Florida

FIGURE 5. Nitza Goldenberg-Cohen, MD (Petah Tikva, Israel), right, after accepting 2003 NANOS Meeting Resident/Fellow Award from Leah Levi, MD (La Jolla, CA).
FIGURE 6. Poster night out at NANOS Snowbird 2003: A: Karl C. Golnik, MD (Cincinnati, OH), Thomas J. Carlow, MD, and Andrew G. Lee, MD (Iowa City, IA). B: Elizabeth Kunsey (West Hartford, CT), NANOS 2003 Meeting Planner, and Cheryl-Ann Tubby (West Hartford, CT), NANOS Executive Director. C: Marilyn C. Kay, MD (Milwaukee, WI), Jacqueline A. Leavitt, MD (Rochester, MN) and Sophia M. Chung, MD (St. Louis, MO). D: Kathleen B. Digre, MD, and Michael C. Brodsky, MD (Little Rock, AR). E: Jonathan C. Horton, MD, PhD (San Francisco, CA), Richard Imes, MD (Alamo, CA), and Klara Landau (Zürich, Switzerland). F: Shalom E. Kelman, MD (Baltimore, MD), Michael Altman, MD (Baltimore, MD) and Nitza Goldenberg-Cohen, MD.

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.
FIGURE 6. Continued.
### Upcoming Meetings

**September 14–18, 2003**
**XVth International Congress of Neuropathology**
Turin, Italy
http://www.newtours.it/icnp2003/
Contact: icnp2003@newtours.it

**December 12–14, 2003**
**Japanese Neuro-Ophthalmology Society**
Kyoto, Japan
http://www.mielparque.or.jp/kyt/kyt01.html
Contact: 81-75-352-7444

**October 8–11, 2003**
**Joint European Research Meeting in Ophthalmology and Vision**
Palacio de Congresos del Colegio Oficial de Médicos.
ALICANTE, Spain
http://www.ever.be
Contact: secretariat@ever.be

**January 28–31, 2004**
**American Society of Neuroimaging 27th Annual Meeting**
Phoenix, Arizona
http://asnweb.org/meeting/meeting2004.shtml
Contact: asm@llmsi.com

**October 9–14, 2003**
**The 25th Pupil Colloquium**
Orthodox Academy of Crete. Kolymbari, Chania, Crete, Greece
Contact: pbitsious@med.uoc.gr

**February 5–7, 2004**
**International Stroke Conference**
San Diego, CA
Contact: strokeconference@heart.org
LaRita Edwards 214-706-1100

**October 18–23, 2003**
**Congress of Neurological Surgeons**
Denver, CO
http://www.neurosurgery.org/cns/meetings/index.asp
Contact: 877.517.1CNS

**March 27–April 1, 2004**
**North American Neuro-Ophthalmology Society (NANOS) Meeting**
Renaissance Orlando Resort at SeaWorld
Orlando Florida
http://www.nanosweb.org/meetings/
Contact: (860) 586-7507

**Oct. 19–22, 2003**
**American Neurological Association**
San Francisco, CA
http://www.anrea.org/
Contact: susanhamilton@msn.com

**April 24–May 1, 2004**
**56th Annual Meeting of the American Academy of Neurology (AAN)**
San Francisco, CA
http://www.aan.com/professionals/index.cfm
Contact: 651-695-1940, web@aan.com

**November 8–12, 2003**
**Society for Neuroscience Annual Meeting**
New Orleans, LA
http://www.sfn.org/
Contact: bj@sfn.org

**April 25–April 30, 2004**
**The Association for Research in Vision and Ophthalmology (ARVO)**
Fort Lauderdale, FL
http://www.arvo.org/
Contact: (240) 221-2900

**Nov. 15–18, 2003**
**American Academy of Ophthalmology Annual Meeting**
Anaheim, CA
http://www.aao.org/annual_meeting
Contact: meetings@aao.org

**May 1–May 6, 2004**
**American Association of Neurological Surgeons 2004 Annual Meeting**
Orlando, FL
http://www.neurosurgery.org/aans/meetings
Contact: 847.378.0500, info@aans.org