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The Optic Neuritis Treatment Trial
Putting the Results in Perspective

Roy W. Beck, M.D., Ph.D. and Jonathan D. Trobe, M.D. for the Optic Neuritis Study Group

The publications of the Optic Neuritis Treatment Trial (1–3) have generated some misconceptions about the study design and the results. In this article, we offer a digest of how the ONTT was conducted, what it showed, how its results may affect management of optic neuritis, and answers to some of the most frequently asked questions about the validity of the results, particularly with respect to the development of multiple sclerosis.

STUDY DESIGN

The ONTT entered 457 patients between July 1988 and June 1991. Entry criteria included a diagnosis of acute unilateral optic neuritis with visual symptoms of eight days or less, age between 18 and 46 years, no previous history of optic neuritis or ophthalmoscopic signs of optic atrophy in the affected eye, no evidence of a systemic disease that might be associated with the optic neuritis, and no previous treatment with corticosteroids for optic neuritis in the fellow eye.

Patients were randomly assigned to one of three treatment regimens: (1) intravenous methylprednisolone (IVMP) 250 mg every 6 h for three days followed by oral prednisone 1 mg/kg/day for 11 days (the intravenous group), (2) oral prednisone 1 mg/kg/day for 14 days (the prednisone group), and (3) oral placebo for 14 days (the placebo group). Regimens 1 and 2 were followed by a short oral prednisone taper consisting of 20 mg on day 15 and 10 mg on days 16 and 18. Whereas patients in the prednisone and placebo groups were masked to their treatment allocation, patients in the intravenous group were not.

Measures of visual acuity, visual field, contrast sensitivity, and color vision were made at seven visits during the first six months, after one year, and then yearly. Highly structured, detailed neurologic examinations were performed at baseline and in follow-up after six months, one year, and then yearly. Additional examinations were performed at times that patients developed symptoms of new neurologic disease or recurrences of optic neuritis. Clinically definite multiple sclerosis (CDMS) was diagnosed when a patient developed a new neurologic event other than a new attack of optic neuritis at least four weeks after study entry with symptoms lasting at least 24 h and documented with objective abnormalities on a neurologic evaluation.

RESULTS

Clinical Characteristics

Mean age of the 457 patients was 32.0 ± 6.7 years; 77% were female and 85% Caucasian. Patients entered the trial within a mean of 5.0 ± 1.6 days from the onset of visual symptoms. Ocular pain, usually worsened by eye movement, was reported by 92%. The optic disc in the affected eye was swollen in 35%.

Treatment Effects

Compared with the placebo group, the intravenous followed by oral corticosteroid regimen pro-
provided a more rapid recovery of vision but no long-term visual benefit (1,2). Most of the difference in rate of visual recovery between groups was seen in the first two weeks. Thereafter, differences in visual function between groups were small. After one year of follow-up, there were no significant differences between the groups in visual acuity, contrast sensitivity, color vision, or visual field (2). The regimen of oral prednisone alone not only provided no benefit to vision but also was associated with an increased rate of new attacks of optic neuritis in both the initially affected and fellow eyes. Within the first two years of follow-up, new attacks of optic neuritis in either eye occurred in 30% of the patients in the oral prednisone group compared with 16% in the placebo group and 14% in the intravenous group.

Unexpectedly, the study found that among the 389 patients with monosymptomatic MS (i.e., not diagnosed as probable or definite MS based on clinical criteria at the time of entry into the ONTT), the intravenous group had a lower rate of development of CDMS within the first two years than did the placebo or prednisone groups (3). CDMS developed within two years in only 7.5% of patients in the intravenous group compared with 16.7% in the placebo group and 14.7% in the prednisone group. The two-year adjusted rate ratio of CDMS in the intravenous group was 0.34 (95% confidence interval 0.16-0.74; p = 0.0063) compared with the placebo group and 0.38 (95% confidence interval 0.17-0.83; p = 0.015) compared with the prednisone group. When the outcome was redefined as either development of CDMS or probable MS or development of CDMS or a new attack of optic neuritis in the fellow eye, the results were similar.

Most of the beneficial treatment effect on the neurologic course was manifested in the patients with an abnormal MRI scan at study entry. Among those patients with two or more MRI signal abnormalities, CDMS developed within two years in 35.9% of 39 patients in the placebo group, 32.4% of 37 patients in the prednisone group, and only 16.2% of 37 patients in the intravenous group. Independent of treatment, the rate of development of CDMS in patients with a normal or nonspecifically abnormal scan was so low that therapeutic efficacy for these patients could not be judged. As expected, the apparent beneficial effect of treatment was not permanent. By the end of the third year of follow-up, the cumulative incidence of definite MS in each group was similar: 17.3% in the intravenous group, 21.3% in the placebo group, and 24.7% in the prednisone group (4).

INTERPRETATION OF NEUROLOGIC RESULTS

Although the study was designed primarily to assess visual recovery, the assessment of MS was a preplanned secondary objective. Recognizing the potential importance of the trial's findings, the ONTT Study Group took exhaustive efforts to evaluate all potential sources of bias, confounding, and errors in data recording or analysis as possible explanations for the surprising treatment effect. These efforts included: (1) review of all neurologic data by a masked observer to classify each patient in regard to whether CDMS had developed, (2) phone contact of patients who had missed the two-year follow-up visit to determine whether any symptoms of MS had developed, (3) survey of examining neurologists to determine whether they had any suspicion of a beneficial treatment effect, (4) assessment of all potential confounding variables, and (5) complete evaluation of the integrity of the dataset and replication of all data analyses at a second biostatistical center.

Several questions have been asked repeatedly in regard to the credibility of the neurologic outcomes in the ONTT. We answer them in the section below.

Did the incidence of MS in placebo-treated patients conform to that of other studies?

Yes. The two-year rate of development of CDMS in the placebo group approximated that of other reported series; therefore, the ONTT findings are that the intravenous group fared better than expected, not that the placebo group fared worse (5-9).

Is there any rationale for the beneficial effect of intravenous corticosteroids on the development of MS?

Yes. There is abundant evidence that MS is an autoimmune disease directed against myelin components. Experimental studies show that lymphokine release up-regulates antigen presentation that may prime lymphocytes recruited to the site of tissue injury (10,11). Such priming may set in motion a continuing or recurring illness. By interfering with lymphokine release, early corticosteroid treatment may prevent this process. Furthermore, by limiting the amplification of antigenic sites (i.e., epitope spreading) that occurs early in the initial attack, immediate immunomodulatory treatment may set the stage for effective intervention later (12-14). Notably, clinical trials with copolymer I and interferon-β have shown greater effectiveness.
in patients in early stages of MS than in patients with chronic progressive MS (15-19).

Why did intravenous corticosteroid treatment exert a beneficial effect while oral prednisone treatment exerted no benefit and actually predisposed to more frequent optic neuritis recurrences?

Although a definitive answer is not available, it is well recognized that high-dose corticosteroid treatment produces immunomodulatory effects that are not seen with low-dose corticosteroid treatment (20). The intravenous regimen may, for example, have achieved higher trough levels that had a greater effect on reducing helper/inducer CD8+ T-cell subsets known to be active in demyelination associated with optic neuritis and MS. The adverse effect of prednisone may have resulted from a preferential reduction in suppressor/inducer CD4+ T-cell subsets (21-24). In experimental allergic encephalomyelitis, Reder et al. (25) demonstrated that varying the corticosteroid treatment regimen can produce markedly different effects on relapse rate.

Wasn't the ONTT designed to assess the effect of treatment on vision rather than on MS?

No. Although the study was designed primarily to measure visual outcome, assessment of the development of MS was a preplanned secondary objective. Board-certified neurologists performed all neurologic examinations at designed intervals and recorded their findings on highly detailed and standardized forms designed with the assistance of an experienced MS investigator (Donald W. Paty, M.D.).

Could the patients in the intravenous group have under reported new symptoms of MS relative to the placebo group?

Unlikely. There is no reason to believe that any patient had a preconceived notion that treatment would benefit the neurologic course. Since visual recovery began quickly in all three groups, there should not have been a greater belief on the part of any patient group that treatment was affecting neurologic status.

Because the neurologists were not completely masked, could they have underinterpreted new symptoms and signs of MS in the intravenous group relative to the other groups?

Unlikely. First, the neurologists were not generally aware of the patient treatment group at follow-up visits. Second, a formal survey of the neurologists provided no indication that they expected treatment to benefit the neurologic course. Third, all of the neurologic examinations were conducted by a detailed, standardized protocol, and completed forms were reviewed in a masked fashion by an authority in MS (Donald W. Paty, M.D.) to ascertain that the appropriate criteria for classification of MS status had been applied.

Could a placebo effect have produced the results?

Unlike. Previous studies have found that immunologic changes can occur in MS patients treated with a placebo (26,27), but it is improbable that the brief intravenous regimen or patient awareness of treatment assignment could have produced physiologic effects powerful enough to account for such a large difference in the rate of MS between groups. Moreover, virtually all patients in all three groups were starting to show improvement in vision after the first few days. Thus, they should all have been expected to believe that they were receiving an active drug.

Could the apparent treatment effect have been due to an imbalance in risk factors among the three groups?

Unlikely. This was extensively evaluated in the data analysis. Controlling for potential confounding variables, including age, gender, race, family history of multiple sclerosis, previous history of optic neuritis in the fellow eye, prior nonspecific neurologic symptoms, and number of signal abnormalities on brain MRI, did not alter the results. In fact, the intravenous group had a slightly higher baseline risk for MS than the other groups; controlling for this increased the magnitude of the treatment effect estimate slightly.

Could the apparent treatment effect have been due to chance?

Unlike. The two-year time period for analysis was preplanned. The p values for the treatment group comparisons were very small. The treatment effect was remarkably consistent across clinical centers and levels of baseline covariates. An effect of similar magnitude to that found at two years was found after six months and one year of follow-up (Table 1).
TABLE 1. Cumulative percentage of ONTT patients with clinically definite multiple sclerosis

<table>
<thead>
<tr>
<th>Time period</th>
<th>Intravenous (%)</th>
<th>Placebo (%)</th>
<th>Prednisone (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>3.1</td>
<td>7.4</td>
<td>7.2</td>
</tr>
<tr>
<td>1 year</td>
<td>6.4</td>
<td>13.4</td>
<td>10.5</td>
</tr>
<tr>
<td>2 years</td>
<td>8.1</td>
<td>17.7</td>
<td>15.6</td>
</tr>
</tbody>
</table>

* Cumulative percentages are from life-table analysis.

What were the conclusions of the independent panel convened by the NIH to review the study results?

The National Institutes of Health review panel (three biostatisticians—Marian Fisher, Ph.D., Daniel Seigel, Ph.D., Roy Milton, Ph.D.—and five MS experts—Stephen Reingold, Ph.D., Henry McFarland, M.D., Kenneth Johnson, M.D., George Ebers, M.D., and John Whitaker, M.D.), shared the study investigators' reservations with regard to the fact that the study had not been primarily designed to assess the development of MS and that the finding was unexpected without a firm physiologic basis. They nevertheless concluded that the results were likely valid and the treatment effect likely real (20), and they recommended that the results should be published.

**IMPLICATIONS FOR CLINICAL PRACTICE**

The two principal treatment recommendations for cases of acute optic neuritis that fit the ONTT clinical patient profile are: (1) oral prednisone treatment should be abandoned, and (2) patients should undergo MRI scans and be treated with intravenous corticosteroid if their scans show two or more signal abnormalities.

Your acceptance of these practices depends on whether you trust the ONTT results (see Interpretation of Neurologic Results, above), and whether you believe that these practices would be practical, cost-effective, and desired by your patients.

With regard to oral prednisone treatment, there should be no issue. At doses used in the ONTT, prednisone is ineffective and possibly harmful, and its use should be avoided. With regard to intravenous corticosteroid treatment, the issues are more complex. You may conclude that the treatment is not worthwhile because the benefit is temporary and does not affect the patient's long-term disability status. Three years after an attack of optic neuritis, ONTT placebo-treated and intravenous-treated patients had similar incidences of CDMS and similar levels of neurologic and visual disability. There is no evidence at present that treatment with intravenous corticosteroids or treatment with other agents would prolong the beneficial effect.

On the other hand, if you believe a low-risk treatment that confers even a temporary benefit is worthwhile, you must decide whether to treat all patients or only those who have abnormal MRI scans. Only one third of the ONTT patients had abnormal scans associated with significant treatment benefit. Therefore, if you elect to treat all patients, you will be offering two thirds of the candidates a treatment without proven benefit and with a small risk of serious harm (28).

A related dilemma is whether to order a brain MRI scan. It is the largest additional expense evoked by the ONTT treatment recommendations, but if you intend to base a treatment decision on the MRI, you must order one. Moreover, MRI clearly offers prognostic information about the chances of developing further neurological events of MS, a result confirmed in other studies (3,29–32).

**Acknowledgments:** Revere Kinkel, M.D., provided considerable input into the section entitled "Is there any rationale for the beneficial effect of intravenous corticosteroids on the development of MS?"

**REFERENCES**


Relative Pupillary Sparing Third Nerve Palsies
To Arteriogram or Not?

Mary Ellen Cullom, M.D., Peter J. Savino, M.D.,
Robert C. Sergott, M.D., and Thomas M. Bosley, M.D.

Ten consecutive patients with acute relative pupillary sparing third nerve palsies were enrolled in a prospective study to determine the prevalence of intracranial aneurysm. All patients were imaged with either cerebral angiography or magnetic resonance angiography. None of the patients demonstrated an intracranial aneurysm. The prevalence of aneurysm in patients with relative pupillary sparing third nerve palsies may be low enough to preclude the use of routine angiography in this condition.

Key Words: Third nerve palsy—Pupil—Arteriogram—Aneurysm.

The "rule of the pupil" has dictated the approach to third nerve palsies in neuro-ophthalmic practice for years. The rule states that when an aneurysm is the cause of a third nerve palsy, the pupil will be dilated and sluggish. Conversely, if the pupillary size and response is normal, aneurysm is unlikely to be the cause of the palsy (1). Therefore, the appropriate management of third nerve palsies is: if the pupil is involved presume there is an aneurysm, perform an MRI or CT scan to exclude a mass, and if no mass, then perform an arteriogram. If the pupil is spared, presume aneurysm is not the cause and proceed with an evaluation for vasculopathic risk factors. In cases of relative pupillary sparing (i.e., when the pupil is only partially involved in a complete external ophthalmoplegia or when the involvement of the extraocular muscles is much greater than the degree of pupillary involvement), the appropriate management is not clearly defined. We conducted a prospective investigation of ten patients with relative pupillary sparing third nerve palsies to try to better define this issue.

MATERIALS AND METHODS

Ten consecutive patients with relative pupillary sparing third nerve palsies were seen in consultation at the Wills Eye Hospital Neuro-ophthalmology Service. Evaluation of each patient included Snellen visual acuity, confrontation visual fields, extraocular motility, pupil size and reactivity, slit-lamp biomicroscopy, and fundus examination. Specifically, pupillary size and reactivity was confirmed by one of the senior neuro-ophthalmic staff (P.J.S., R.C.S., T.M.B.). After the diagnosis of an isolated relative pupillary sparing third nerve palsy was made, the patients were imaged by either CT or MRI scan to exclude an intracranial
mass. Nine patients then underwent cerebral arteriography, and one patient underwent magnetic resonance angiography (MRA) because she was not systemically well enough to be subjected to cerebral arteriography. MRA, with high spatial resolution, is thought to be sensitive to aneurysms which are larger than 3 mm in diameter (2,3). In no case did a patient have an evolving third nerve palsy after initial presentation.

Eight patients were male and two female. The age range of the patients was 52-77 years of age; the mean age was 66 years. Eight of ten patients were hypertensive and four of ten had diabetes mellitus. Eight of the palsies were left-sided and two right-sided. Eight of the ten patients experienced either a dull ache around the affected eye or a headache on the affected side (Table 1).

CASE REPORTS

Case 2

A 67-year-old woman with hypertension, angina, asthma, and diverticulitis presented with a three-week history of left frontoparietal headache and an eight-day history of left-sided ptosis. Best corrected visual acuity was 6/9 in each eye. Visual fields were full to confrontation. There was complete ptosis on the left. Extraocular motility was full in the right eye. Motility in the left eye showed full abduction, 0% adduction, 30% elevation, and depression (Fig. 1). The right pupil was 3 mm in room light and constricted briskly to 2 mm with bright light. The left pupil was 5 mm in room light and constricted sluggishly to 3 mm with bright light. Slit-lamp biomicroscopy and fundus examination were normal.

An MRI showed small-vessel ischemic change. A cerebral arteriogram of the right and left internal carotid arteries and left vertebral artery was normal. The patient was last seen two months after initial presentation, only 1 mm of left-sided ptosis remained, extraocular motility was full in both eyes, pupil size was 3 mm OD and 4 mm OS, and there were no signs of aberrant regeneration.

Case 3

A 69-year-old woman with hypertension, diabetes mellitus, and hypothyroidism presented with binocular diplopia, left ptosis, and a dull ache OS for two weeks. Best corrected visual acuity was 6/9 in each eye. Visual fields were full to confrontation. There was 2 mm of left-sided ptosis. Extraocular motility was full in the right eye. Motility in the left eye showed full abduction, 30% adduction, 70% elevation, and 60% depression. The right pupil was 3.5 mm and constricted briskly with bright light. The left pupil was 4.5 mm and reacted sluggishly to bright light. Slit-lamp biomicroscopy and fundus examination were normal.

An MRI was normal. An MRA was performed which showed no evidence of aneurysm. The patient was seen three months after initial presentation, the left ptosis had resolved, extraocular motility was full in both eyes, pupil size was 3.0 mm OD and 4.0 mm OS, and there were no signs of aberrant regeneration.

Case 7

A 52-year-old man with hypertension and diabetes presented with left-sided headache, left ptosis, and diplopia for one week. Best corrected visual acuity was 6/12 in the right eye and 6/21 in the left eye. Visual fields were full to confrontation. There was 75% ptosis of the left upper lid. Extraocular motility was full in the right eye. Motility in the left eye showed full abduction, 5% adduction, 15% elevation, and 15% depression. The right pupil was 5 mm in room light and constricted briskly to 3 mm with bright light. The left pupil was 7 mm in room light and constricted sluggishly to 5 mm with bright light. Slit-lamp biomicroscopy was normal. Fundoscopic examination revealed background diabetic retinopathy in both eyes and panretinal photocoagulation scars in the periphery of the left fundus.

A CT scan was normal. A left internal carotid arteriogram was performed and failed to demonstrate an aneurysm. The patient was last seen four years after initial presentation, the left-sided ptosis had completely resolved, extraocular motility was full in the left eye, pupillary size was 4 mm OU, and there were no signs of aberrant regeneration.

DISCUSSION

Evidence to support the “rule of the pupil” is abundant in the literature. In a series by Green et al. (3), 36/38 patients with third nerve palsies secondary to cerebral aneurysms had pupillary involvement. Rucker (4) reported sphincter impairment in 62/64 cases of aneurysm. Despite these series that have provided the foundation for the rule of the pupil, there are numerous reports of patients who have not obeyed the rule. Patients have presented with pupillary sparing third nerve palsies and were found to have internal carotid, posterior communicating, and basilar artery aneu-
### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Pt./age (yr)/sex</th>
<th>Medical history</th>
<th>Eye</th>
<th>Ocular history</th>
<th>Visual acuity</th>
<th>Pupil size (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/54/M</td>
<td>Hypertension</td>
<td>OD&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Ptosis OD, diplopia ×1 day</td>
<td>6/12</td>
<td>8.0</td>
</tr>
<tr>
<td>2/57/F</td>
<td>Hypertension, coronary artery disease mitral valve prolapse, asthma</td>
<td>OS&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Left sided headache ×3 weeks</td>
<td>6/9</td>
<td>5.0</td>
</tr>
<tr>
<td>3/59/F</td>
<td>Hypertension, diabetes mellitus, hypothyroid</td>
<td>OD&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Dull ache OS ×2 weeks</td>
<td>6/9</td>
<td>3.0</td>
</tr>
<tr>
<td>4/55/M</td>
<td>Hypertension</td>
<td>OS&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Ptosis OS ×2 weeks</td>
<td>6/7.5</td>
<td>4.5</td>
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<tr>
<td>5/62/M</td>
<td>Hypertension, diabetes mellitus, tuberculosis, peptic ulcer disease</td>
<td>OD&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pain OD, ptosis OD, diplopia</td>
<td>6/7.5</td>
<td>5.0</td>
</tr>
<tr>
<td>6/57/M</td>
<td>Hypertension, diabetes mellitus, gout</td>
<td>OD&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pain OS, diplopia ×1 week</td>
<td>6/6</td>
<td>3.5</td>
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<tr>
<td>7/52/M</td>
<td>Hypertension, diabetes mellitus, arthritis</td>
<td>OD&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Left sided headache, ptosis</td>
<td>6/12</td>
<td>5.0</td>
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<tr>
<td>8/73/M</td>
<td>Dysplastic nevi</td>
<td>OD&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Dull ache OS, ptosis OS, diplopia ×1 week</td>
<td>6/7.5</td>
<td>4.5</td>
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<tr>
<td>9/51/M</td>
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<td>OD&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Ptosis OS, diplopia ×2 days</td>
<td>6/9</td>
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<td>6.0</td>
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</table>

<table>
<thead>
<tr>
<th>Pt./age (yr)/sex</th>
<th>Lids</th>
<th>Motility</th>
<th>Arteriogram (vessels injected/results)</th>
<th>Complications</th>
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<tbody>
<tr>
<td>1/54/M</td>
<td>Complete ptosis</td>
<td>0% add, 20% elev, 0% dep, 100% abd</td>
<td>Right carotid, left vertebral</td>
<td>None</td>
</tr>
<tr>
<td>2/57/F</td>
<td>Normal</td>
<td>Full</td>
<td>Complete right internal carotid occlusion</td>
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<tr>
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<td>Full</td>
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</tr>
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<td>4/55/M</td>
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<td>Full</td>
<td>Left internal carotid, left vertebral</td>
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<tr>
<td>5/62/M</td>
<td>Moderate ptosis</td>
<td>10% add, 40% elev, 80% dep, 100% abd</td>
<td>Right internal carotid</td>
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<td>6/57/M</td>
<td>Normal</td>
<td>Full</td>
<td>Left internal carotid, left vertebral</td>
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<tr>
<td>7/52/M</td>
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<td>Full</td>
<td>Left internal carotid</td>
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<td>8/73/M</td>
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<td>Left internal carotid</td>
<td>None</td>
</tr>
<tr>
<td>9/51/M</td>
<td>Complete ptosis</td>
<td>0% add, 10% elev, 10% dep, 100% abd</td>
<td>Left internal carotid, left vertebral</td>
<td>Negative</td>
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<tr>
<td>10/77/M</td>
<td>Normal</td>
<td>Full</td>
<td>Left internal carotid, left vertebral</td>
<td>None</td>
</tr>
</tbody>
</table>

<sup>a</sup> M = male, F = female; OD = right eye, OS = left eye; add = adduction, abd = abduction, dep = depression, elev = elevation.
<sup>b</sup> Denotes affected eye.
THIRD NERVE PALSIES

In 1983, Kissel and associates (5) published a retrospective review of internal carotid-posterior communicating artery aneurysms. At presentation 21/51 patients had partial oculomotor palsies. Of these partial oculomotor palsies, 14/21 had pupillary involvement at the onset of the palsy and five of the remaining seven progressed to pupillary involvement. Three of 51 patients with aneurysm had relative pupillary sparing.

In addition to patients with aneurysms presenting with pupillary sparing, those with vasculopathic third nerve palsies demonstrating some degree of sphincter impairment are also common in the literature. In Green’s series (3), 8/25 patients with diabetic third nerve palsies had pupillary involvement. Of the eight patients with pupillary involvement, four had a dilated and fixed pupil and four had a dilated and reactive pupil. Rucker (4) reported that in patients with vasculopathic third nerve palsies, 11/63 patients showed pupillary abnormalities. In Goldstein and Cogan’s (8) series of diabetic ophthalmoplegia, 5/22 patients had pupillary involvement, and four of these five appeared to have relative pupillary sparing.

It is clear that there is considerable overlap in clinical presentation of patients with third nerve palsies secondary to aneurysms and those due to microvascular disease. There exists a subset of patients that does not fit strictly into one of the two categories of complete pupillary involvement or complete pupillary sparing. These are the patients that present with partial or complete external ophthalmoplegia with some degree of, but not total, pupillary involvement (i.e., relative pupillary sparing).

This clinical overlap can make it difficult to determine the appropriate management of the patient that presents with relative pupillary sparing. The major diagnostic decision is whether to subject the patient to cerebral arteriography, with its attendant risks, to exclude an intracranial aneurysm. The reported morbidity of cerebral arteriography ranges from 0.0% to 28% and variability among institutions is high. In recent years, there has been a trend toward lower complication rates (9-12). The morbidity of arteriography must be weighed against the probability of identifying a treatable lesion.

Our ten consecutive patients with relative pupillary sparing third nerve palsies were free of aneurysm on cerebral angiography or MRA. None of the patients experienced a complication secondary to invasive imaging.

We recognize that the number of patients enrolled in this study is small; however, this is an uncommon condition. There may also be a selection bias since all patients presented as outpatients to a neuro-ophthalmology service and seven of ten patients had symptoms for more than one week. This type of presentation may be selecting for patients free of intracranial pathology. As previously stated, all patients were in the vasculopathic age
group; in a younger subset of patients, the incidence of aneurysm may be higher.

Until now, the appropriate management of patients with relative pupillary sparing third nerve palsies was not clearly defined. Most neuro-ophthalmologists tended to consider this entity as pupillary sparing and treated patients conservatively. Our study appears to support this behavior; it appears that the incidence of aneurysm in this subset of third nerve palsies is low. We recognize that it has been reported that patients with relative pupil sparing may harbor an intracranial aneurysm (5). However, the incidence of aneurysm may be low enough to preclude the need for routine cerebral angiography in this group of patients. The exact role for MRA in detecting aneurysms smaller than 3 mm awaits further clarification.

**REFERENCES**


Commentary: Isolated Incomplete Third Nerve Palsies in the Vasculopathic Age Group: To Angiogram or Not to Angiogram—That Is the Question.

In this issue of the journal, Cullom et al. propose that "the prevalence of aneurysm in patients with relative pupillary sparing third nerve palsies may be low enough to preclude the use of routine angiography." The paper obviously attempts to address a well-known problem: how to manage third nerve palsies that do not fit the rule of the pupil? The rule of the pupil applies to patients in the vasculopathic age group who have acute, isolated oculomotor palsies with complete external ophthalmoplegia. In such patients, obvious pupillary involvement (mydriasis, poor reactivity) warrants emergent noninvasive imaging, followed, if negative, by cerebral angiography in search of a "posterior communicating artery" aneurysm. Pupillary sparing (no anisocoria, normal reactivity) is assumed to imply small vessel ischemia (mononeuropathy multiplex) and is managed medically/conservatively. When the rule of the pupil does not apply, i.e., when either the ophthalmoplegia and/or pupillary involvement is incomplete, the clinician's dilemma becomes whether to angiogram or not to angiogram. No reliable guidelines exists on how to manage incomplete third nerve palsies. Without such guidance, neuro-ophthalmologists at times make difficult decisions based more on the art than the science of medicine. Sometimes the concept of "relative pupil sparing" is invoked; however, that is an entity which unfortunately does not have a uniformly accepted definition. Cullom et al. seem to have a very liberal definition of relative pupil sparing, allowing for incomplete extraocular muscle paresis with or without some pupillary involvement. It is my bias that a relative pupil sparing oculomotor palsy exists when there is complete external ophthalmoplegia and only minimal pupillary involvement, i.e., the pupillary abnormality is disproportionately mild when compared to the otherwise complete paralysis of the extraocular muscles. When the latter definition is met, some neuroophthalmologists, perhaps with trepidation, manage the patients conservatively on the assumption that the etiology is vasculopathic, nonaneurysmal and therefore not deserving emergent cerebral angiography.

Practically every conceivable variation on the theme of a partial ophthalmoplegia and pupillary abnormality has been reported as a manifestation of aneurysmal compression; therefore prudence
would suggest that angiography should be the rule rather than the exception in cases that do not obey the rule of the pupil. Since every acute incomplete third nerve palsy is a potential harbinger of impending aneurysmal rupture, it would be very helpful to know how frequently incomplete oculomotor palsies is due to an aneurysm. A large, preferably prospective series is needed to provide information about the incidence of aneurysm in patients with partial oculomotor palsy. What is troublesome about the paper by Cullom et al. is that it draws conclusions on the basis of a very small patient sample. A series of ten cases is so small that it provides insufficient guidance on how to manage patients. If the authors' next clinical case proved to be aneurysmal, then they would have to conclude that the incidence of aneurysm with relative pupillary sparing (as defined in their paper) is close to 10%. Such statistics would clearly argue in favor of proceeding with cerebral angiography in their cases.

In short, the conclusions of the paper by Cullom et al. are based on too small a sample and therefore their recommendations are premature. What is needed is the publication of a much larger series evaluating patients in the vasculopathic age group presenting with acute, isolated incomplete oculomotor palsies. Such a study could provide data about the incidence of aneurysm as well as about the potential prognostic difference between pupil-sparing and pupil-involving partial third nerve palsies. A well-designed, prospective study could perhaps best be completed by combining data from several institutions represented by readers of the journal. Until the recommendations of Cullom et al. are confirmed by such a study, it appears prudent to err on the side of ordering too many rather than too few angiograms.

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Commentary

If it is true that there is considerable overlap in the clinical presentation of patients with oculomotor pareses, be they aneurysmal or microvascular, how is the clinician to behave when such patients are evaluated? To arteriogram, or not? The paper by Cullom et al. published in this journal suggests that one may err on the side of caution—that is, angiography is not imperative—when there is relative pupillary sparing. From a series of ten, these authors argue that relative pupillary sparing may be treated as pupil sparing. They base this supposition upon reasoning that the incidence of aneurysm in this subset of third nerve palsies is low, indeed, low enough to preclude the use of routine angiography. We disagree with these conclusions.

Given that the authors admit "it has been reported that patients with relative pupillary sparing may harbor an intracranial aneurysm," and given Kissel's published observations that three of 51 patients with aneurysm and oculomotor weakness had relative pupillary sparing, we believe to err on the side of caution is to do the angiogram. For the clinician seeing and taking care of patients, it is imperative to separate what one thinks and how one behaves. We may think the likelihood of an aneurysm to be low, but we must behave in a manner that does not overlook its presence. The yield of finding an aneurysm in the patient whose pupil is partially spared yet shows third nerve involvement may be lower than previously thought, but not to uncover an aneurysm that is changing and causing a new cranial neuropathy may on more than an occasional basis be disastrous for that patient. It is an error of omission that ought not be made in this day and age.

Recognizing the aneurysm allows us to treat a cause of stroke, perhaps the most treatable cause of stroke; while more patients will be angiogramed than aneurysms discovered, for the patient with the aneurysm, prognosis ought be dramatically changed by its recognition and successful remedy. A converse statement is also true: for the physician who fails to recognize an aneurysm in the patient presenting with new cranial neuropathy, his future too would be clouded. We therefore take the opposite perspective of the authors of this paper, and say, for the average clinician, considering your average third nerve paresis, the differentiation should be, is the pupil involved or is it not? If it is involved at all, be it minimally, relatively, or sparingly, a compressive lesion (statistically most likely an aneurysm) must be ruled out. While this rule is not inviolate, we ask that it only be violated by the neuro-ophthalmologist, not the general community of practicing physicians.

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The Treatment of Superior Oblique Myokymia Utilizing the Harada-Ito Procedure

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A woman with superior oblique myokymia (SOM) was cured of her condition by performing a Harada-Ito procedure. This procedure involves transposing the anterior portion of the superior oblique tendon, which is responsible for cyclorotation, nasally to create an effective weakening of the anterior portion of the tendon instead of temporal displacement utilized for superior oblique paresis. We measured the patient's eye movements before and after surgery, using the magnetic search coil technique, and confirmed that (1) the SOM was abolished and (2) vertical eye movements, including saccades, were unaffected.

Key Words: Superior oblique myokymia—Harada-Ito procedure.

CASE REPORT

A 38-year-old Caucasian woman first presented to the Cleveland Clinic on April 15, 1992, with a
1-year history of episodic "quaking" of her right eye. This phenomenon was made worse by stressful situations, and, although she could control it with concentration, she could not do this for long periods of time. These episodes would occur at a rate of approximately 3-4 Hz when present. She denied any vertical imbalance in the visual environment but did note that things would "tilt." She had no significant past medical history except for thyromegaly with normal thyroid function tests. She had no previous problems with her vision.

Her ophthalmic examination was unremarkable except for obvious intorsional movements of her right eye on slit lamp examination typical for SOM. A magnetic resonance imaging (MRI) scan failed to reveal any abnormalities. Tegretol was titrated to a level of 800 mg per day with minimal effect on her symptoms. A trial of Inderal 80-LA likewise failed to relieve her symptoms. Dilantin at a dose of 800 mg per day was discontinued as it made the patient drowsy. Therefore, on March 31, 1993, she underwent an Harada-Ito procedure and after a brief recovery period she noted no further episodes of SOM and her ocular motility remained full. She has been free of symptoms after 1 year of follow-up.

**SURGICAL PROCEDURE**

A limbal-based incision of four clock-hours was made superiorly in the right eye under local anesthesia. The superior rectus muscle was grasped with a small and then a square muscle hook. A small muscle hook was then used to grasp the superior oblique tendon and expose it temporal to the superior rectus muscle. A 6-0 Vicryl suture was placed into the anterior portion of the superior oblique tendon, after which this portion of the tendon was cut with Wescott scissors. The tendon was then split down the longitudinal axis in order to create a free segment. This free segment of tendon was then placed 5 mm nasal to the insertion of the superior rectus muscle and 7 mm behind the limbus (Fig. 1). The conjunctiva was then injected with 100 mg of Ancef without suturing the conjunctiva. The patient was placed on Maxitrol drops four times a day for 5 days postoperatively.

**METHODS**

Horizontal, vertical, and torsional rotations of both eyes were recorded using 6-ft magnetic field coils (CNC Engineering, Seattle, Washington) and search coils consisting of silastic scleral annuli (Skalar, Delft, Netherlands), as previously described (11,12). The system was 98.5% linear over the operating range of ±20 degrees in all three planes and, for the amplifier settings used, the standard deviation (SD) of the noise of the system was less than 0.05 degrees. We measured attempted binocular fixation of a laser spot projected onto a tangent screen, and horizontal and vertical saccades in response to ±15 degrees step displacements of the target. In addition, we measured smooth-pursuit and vestibular eye movements as previously described (13). Data were filtered, digitized at 200 Hz, and analyzed interactively, as previously described (11,14). Because of the inherent variability of torsional gaze over several seconds (15), and the small amplitude and velocity of the movements of SOM, we mainly used inspection of the records (see Figs. 2 and 3), buttressed by plots of the relative amplitudes of the Fourier coefficients at frequencies from 0 to 50 Hz to detect SOM.

**RESULTS**

Prior to surgery, frequent episodes of SOM occurred; an example is shown in Fig. 2B. Note how fixation is relatively steady in the left eye, but the vertical and torsional channels show gaze instability typical of SOM (3,11,16,17). Fourier analysis of the torsional movements showed increased coefficients up to 50 Hz in the right eye compared with the left, typical of SOM. Also shown in Fig. 2 are some typical vertical saccades prior to surgery.
FIG. 2. (A & B) Representative, corresponding 1-second records from the left and right eyes of the patient during a typical episode of SOM. Note how the vertical and torsional position (arrows) of the right eye is disrupted by SOM. (C & D) Corresponding records of some typical vertical saccades of the left and right eyes. The peak-velocity to amplitude relationship of these saccades was normal (see text). Note that in this and the following figure that upward deflections indicate eye rotations rightward, upward, or clockwise with respect to the subject.

these have normal peak-velocity to amplitude relationships. For example, the first downward saccade in Fig. 2C and D was about 31 degrees in both eyes, and had peak velocity of 444 degrees per second in the left eye and 423 degrees per second in the right eye. After surgery, no episodes of SOM were recorded or subjectively reported; an example of the fixation characteristics is shown in Fig. 3A and B. Fourier analysis of the torsional movements showed similar coefficients in the two eyes. In addition, vertical saccadic velocities were unaffected. For example, the last downward saccades of Fig. 2C and D were about 32 degrees in both eyes, and had peak velocity of 463 degrees per second in the left eye and 461 degrees per second in the right eye.

DISCUSSION

In 1964, Harada and Ito described a new surgical treatment of SOM (18). They suggested that the superior oblique tendon was functionally divided into two separate aspects. The posterior portion of the tendon was responsible for the depressor aspect, while the anterior portion was responsible for the torsional aspect. Patients with superior oblique palsy who had a large and symptomatic torsional deviation could be successfully treated by temporally displacing the anterior portion of the tendon that created an effective strengthening of the torsional aspect with relief of the torsional symptoms. This procedure did not alter the depressor function of the tendon and therefore did
not induce a hypertropia. They proposed that
1. Anterior partial advancement of the superior oblique results in intorsion.
2. Anterior partial recession of the superior oblique muscle results in extorsion.
3. Anterior partial advancement of the inferior oblique muscle results in extorsion.
4. Anterior partial recession of the inferior oblique muscle results in intorsion.

None of these aspects alters the vertical function of these oblique muscles (8,19).

Although the Harada-Ito procedure was effective in abolishing the SOM in our patient, vertical saccades were unaffected. It appears that the superior oblique muscle contributes little to the velocity of vertical saccades in any field of gaze, since Stathacopoulos and colleagues (20) showed that the velocity of vertical saccades was not reduced in patients with superior oblique palsy.

The etiology of SOM is unknown (2,4,9,21,22), although quantitative records and electromyo-graphic recordings from the superior oblique muscle have been interpreted as indicating neuronal damage and subsequent regeneration (23-25). Experimental lesions of the trochlear nerve have demonstrated a considerable capacity for regeneration (25). One possibility is that mild damage to the trochlear nerve could trigger the mechanism for maintaining a constant number of axons in the nerve; some of these cases may be predisposed to SOM.

Our patient had no evidence of multiple sclero-
sis, which infrequently presents with SOM (3). Although a normal MRI scan does not eliminate multiple sclerosis as a diagnostic possibility, our patient had no other signs or symptoms of this disorder. Our patient failed to respond to multiple medications typically used for SOM, and this led us to utilize a surgical option. We do not know if this procedure will work for all patients experiencing SOM. However, we are encouraged by this initial success and present this surgical procedure as an option for the treatment of this enigmatic disorder.

REFERENCES

Intermittent Esotropia Associated with Rippling Muscle Disease

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Abstract:

Purpose: We report a rare myopathy known as rippling muscle disease, with the unique feature of extracranial muscle involvement, presenting as a variable esotropia.

Methods: Chart review with a review of the literature.

Results: Neurologic and neuro-ophthalmic examinations as well as electromyography and muscle biopsy confirm that this case closely resembles those described in the literature with the additional feature of a variable esotropia.

Conclusion: Rippling muscle disease may be associated with intermittent esotropia. The pathophysiology of this disorder is unknown, but the intermittent esotropia is likely related to "rippling" of the medial recti.

Key Words: Rippling muscle—Esotropia.

Torbergsen in 1975 (1) described a family with a disease resembling myotonia congenita but distinct from it in significant respects. Since then, a number of authors have reported similar cases of a disorder whose essential features consist of muscle stiffness after periods of rest, a local mounding phenomenon on percussion of muscles, wave-like fasciculation of muscles on active contraction, stretching, on percussion that is electrically silent, and nonspecific findings on muscle biopsy. In all of the cases described, the process spared the cranial musculature except for occasional percussion myotonia of the tongue. Our patient had involvement of the extraocular muscles with intermittent, involuntary contraction of the medial recti, creating an intermittent esotropia.

CASE REPORT

A 58-year-old white man was referred to the neuromuscular service of the Cleveland Clinic Foundation on February 2, 1992. He complained of a symmetrical weakness of his arms and legs. His problem started about a year before presentation when he dropped a ladder while at work because of weakness in his arms. Other symptoms consisted of a "rippling" phenomenon in his muscles when he tapped them. There was pain and stiffness in his thighs on prolonged sitting. Occasionally his tongue seemed to feel thickened, and his speech seemed to become slurred. During the course of the year, he had developed intermittent diplopia that progressively worsened. The diplopia was worse on awakening and when fatigued.

His past medical history was significant for a myocardial infarction in 1980 and a coronary artery bypass graft in 1989. He drank about a case of beer a day until 2 months before presentation, when he abstained. He was employed as a metal plant in-
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spector where he was exposed to solvents used in titanium processing. However, all of the titanium was removed by the time he inspected the product. He had no knowledge of any relatives or coworkers with a similar disorder.

General physical examination was unremarkable. The muscular disorder consisted of active visible contractions that were associated with a painful sensation. The muscle spasms were clinically obvious as a “rolling dimpling” of the skin. The typical wave-like rippling of the muscles was best observed on tapping his brachioradialis. On repeated tapping of his muscles, the rippling phenomenon gradually became less prominent. Percussion of the large muscle bellies produced rapid contraction without dimpling. (Fig. 1) Active contraction produced giant dissipating fasciculations. Deep palpation of the muscles, especially the pectoralis major, produced a mounding phenomenon that gradually dissipated. His hand-grip release was normal. Percussion myotonia of the tongue was noted. There was a mild diminution of vibration of the toes bilaterally.

Review of his outside laboratory investigations revealed an elevated creatinine phosphokinase (676 IU), mildly elevated Westergren sedimentation rate (WSR) (30 mm/h), negative antibody to nucleic acid (ANA) and a negative rheumatoid factor (RF). The rapid plasma reagin (RPR) was non-reactive, and a thyroid profile was normal. Magnetic resonance imaging (MRI) of the brain was normal.

He was referred to the neuro-ophthalmology service for evaluation of his diplopia. His ocular examination revealed best corrected visual acuities of 20/15. The pupils were 4 mm in diameter, reacted briskly, and there was no afferent pupillary defect. In the primary position, there was a 6 diopter intermittent esotropia that increased to 20 diopters in right gaze and to 10 diopters in left gaze but was quite variable. At times he would be orthophoric. He developed a medial rectus “spasm” with prolonged near gaze that he was not able to break easily when going from near to distance viewing (Fig. 2). Coinciding with the spasm, he felt a "tugging" sensation around his eyes that was similar to the discomfort that he felt in his other muscles. These episodes could also be completely spontaneous but were most easily provoked by a near stimulus. The episodes were unassociated with pupillary miosis as seen in spasm of the near reflex. There was no evidence of ophthalmoplegia.

FIG. 1. Demonstrating the dissipating fasciculation of the forearm muscles on percussion. In the first frame, the patient induces the contraction by sharply tapping his brachioradialis. The next two frames show the progressive contraction of the brachioradialis.
nystagmus, or fatigable weakness. External, slit-lamp, and fundus examinations were unremarkable.

Laboratory investigations revealed a creatine phosphokinase (CPK) between 293 and 378 IU with a MM fraction of 95%. His thyroid profile was normal and the WSR was 20 mm/h. The complete blood count and urinalysis were normal, and his liver enzymes had normalized except for mild elevation of alkaline phosphatase at 130 U (normal, 20-120 U). His electromyogram revealed normal nerve conduction and needle examinations with no evidence of electrical myotonia or membrane irritability. The rolling-muscle phenomenon was electrically silent.

**PATHOLOGY**

The 10% formalin-fixed and parafin-embedded tissue sections of the left vastus lateralis muscle were cut 4 μm thick. Sections were stained with hematoxylin eosin. Frozen tissue segments of skeletal muscle were cut and stained with H&E, NADH, cytochrome oxidase, Masson trichrome, periodic acid–Schiff (PAS), adenosine triphosphatase (ATP-ase) (pH 4.6 and 9.8), nonspecific esterase, oil-red-O, acid phosphatase, alkaline phosphatase, and sulfonated alcian blue stains. Rare focal interstitial and perivascular chronic inflammation consisting primarily of lymphocytes was present (Fig. 1). There was no evidence of vasculitis or granulomas. Acid phosphatase staining showed rare regenerating muscle fibers. Scattered angular atrophic esterase-positive muscle fibers were present (Fig. 2). Focal areas of small-group atrophy were also present. ATP-ase staining demonstrated that the atrophic muscle fibers were both type I and II. There appeared to be a prominent type IIB muscle fiber atrophy (the patient never took corticosteroids). There was no evidence of fiber type grouping on the ATP-ase stains. Mild focal disruptions in the architecture were noted on the NADH and cytochrome oxidase stains. Rimmed vacuolar inclusions suggestive of inclusion body myositis were not seen on the trichrome stain. There was no evidence of amyloid on the sulfonated alcian blue stain. No abnormalities of glycogen or lipid were noted on the PAS and oil-red-O stains, respectively.

Electron microscopy revealed “honeycomb-like” structures beneath the sarcolemma (Fig. 3). These structures could not be identified as emanating from any particular muscular substructure. Their origin and function(s) are unknown. However, these identical structures have been reported in other cases of RMD.

**DISCUSSION**

Torbergsen (1) described a family of 32 members, five of whom had muscle stiffness, mounding of muscles on percussion (myoedema), generalized muscular hypertrophy, rolling muscle contractions on mechanical stimuli, and myotonia-like reactions to percussion of the thenar eminence. The disorder had an autosomal dominant inheritance. Ricker et al. (2) described six patients from two families having the same autosomal dominant disorder. Alberca et al. (3) reported a sporadic case with similar features who also had some speech difficulties and what they thought was an independent cerebellar atrophy. Jusic (4) described a mother and son with a similar disorder who developed progressive muscular contractures, begin-
FIG. 3. A: Skeletal muscle with peri-vascular chronic inflammation consisting mostly of lymphocytes (arrow). Scattered atrophic fibers are also present. (Hematoxylin and eosin, ×20.) B: Nonspecific esterase stain showing scattered angular atrophic positive-staining fibers indicative of acute neurogenic atrophy. (Esterase, ×10.) C: Honeycomb-like subsarcolemmal structures.

ning with the fingers. They also had percussion myotonia of the tongue and chronic sensorimotor polyneuropathy. Sadeh et al. (5) described a father and son with the same findings, except for the absence of wave-like contractions. They found multiple vacuoles on electron microscopy that they thought represented dilations of the T-tubules. They hypothesized that the honeycomb structures described by Ricker (2) and Alberca (3) represented the same vacuoles. Rao et al. (6) described a similar sporadic case in a black teenager.

The characteristic features described by Torbergsen and subsequent authors, such as muscle stiffness, mounding phenomenon (myoedema), electrically silent rippling of muscles, absence of myotonia on electromyogram (EMG), moderately elevated CPK, and nonspecific findings of a myopathy on muscle biopsy were all present in our patient.

Recent genetic investigations performed by Stephan et al. (7) revealed a strong linkage of RMD to the 1q41 locus. It appears that in at least one Oregon family, the genetic locus is within a 12-cM region between the D1S235 and D1S163 markers. These researchers were able to exclude the genes for the subsarcolemmal voltage-sensitive Ca^{2+} (DHP-receptor), sarcoplasmic reticulum Ca^{2+}-induced release channel (ryanodine receptor), myotonic dystrophy kinase, and the voltage-sensitive muscle sodium channel as causes of this disorder. Further, they analyzed the German family reported by Ricker and were unable to identify the same genetic loci, thereby indicating genetic heterogeneity in RMD.

Symptomatically, our patient's diplopia was the most troublesome feature. Ocular examination revealed a variable intermittent esotropia. Active, involuntary contraction of his medial recti, particu-
larly with near viewing, resulted in spasms that he found difficult to break on subsequent distance viewing. He needed to blink once or twice to relieve his diplopia. He had a sense of discomfort with this esotropia.

We believe that his ocular symptoms were due to involvement of his medial recti by the same process that affected his skeletal musculature. The parallel time course, clinical similarity of spasm on active contraction, and discomfort are all in favor of this supposition. Percussion myotonia of his tongue indicates involvement of other cranial muscles. An EMG of the medial recti to demonstrate electrical silence was considered to prove this phenomenon; however, in the absence of a definitive treatment, the patient declined.

Given the variability of his esotropia, recessions of the medial recti could not be expected to improve his diplopia. Calcium channel blockers have been shown to have some efficacy in affected patients. To date, this form of therapy has not improved our patient's intermittent diplopia.

REFERENCES

Angiocentric T-Cell Lymphoma Presenting with Multiple Cranial Nerve Palsies and Retrobulbar Optic Neuropathy

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Angiocentric T-cell lymphoma (lymphomatoid granulomatosis) may present with prominent central nervous system (CNS) findings with variable radiographic features. We describe a patient who presented with multiple cranial nerve palsies involving the left optic nerve, left facial nerve, left ocular motor nerves, and bilateral acoustic nerves. Enhancement of the right temporal meninges and a cavernous sinus mass were noted on magnetic resonance (MR) scan. A right temporal craniectomy and meningeal biopsy were performed. Meningeal biopsy revealed atypical angiocentric granulomatous lymphoid infiltrates without associated necrosis, giant cells, or granuloma formation. Morphologic and T-cell receptor gene rearrangement findings were diagnostic of an angiocentric T-cell lymphoma. Retrobulbar optic neuropathy and multiple cranial nerve palsies may be the presenting features of angiocentric T-cell lymphoma. The neurologic and unique radiographic changes in our case expand the previously reported findings in CNS angiocentric T-cell lymphoma.

Key Words: Lymphoma—Lymphomatoid granulomatosis—Retrobulbar optic neuropathy—Multiple cranial nerve palsies.

Angiocentric immunoproliferative lesions (AIL) are angiocentric, destructive lymphoproliferative diseases that are characterized neither by multinucleated giant cells nor by true granulomas (1,2). Lymphomatoid granulomatosis lies at the higher-grade end of the histologic spectrum of AIL and should probably be considered a malignant angiocentric T-cell lymphoma from onset (1-3). Although angiocentric T-cell lymphoma usually affects the lungs, other sites, such as the kidney, skin, upper respiratory tract, and peripheral nerve, may be involved (4,5). The central nervous system (CNS) is involved in approximately 30% of cases with varying clinical presentations (2,4). Most primary CNS lymphomas are of B-cell origin and present with discrete masses; angiocentric T-cell lymphomas are much less common and often present with a diffuse “vasculitic” CNS process.

We present a case of biopsy-proven angiocentric, angiodestructive T-cell lymphoma in a patient who presented with multiple cranial neuropathies, a severe retrobulbar optic neuropathy, enhancement of the right temporal meninges, and a cavernous sinus mass on magnetic resonance (MR) scan.

CASE REPORT

A 71-year-old man was evaluated for visual and hearing loss and facial paresis. In April 1991, he noted progressive bilateral hearing loss, especially on the left. In December 1991, he developed a complete, painless visual loss on the left. Ophthalmic examination revealed a left relative afferent pupil-
lary defect and an acuity of 20/200 OS. Funduscopic examination was essentially normal, and a diagnosis of "retrobulbar optic neuropathy of unknown cause" was made. In February 1992, he noted difficulty in closing his left eye and was diagnosed as having a left peripheral cranial nerve VII paresis. At that time, he also noted low-grade fever, occasional night sweats, and arthralgias especially affecting his knees. Work-up at another institution revealed a sedimentation rate of 120 mm but temporal artery biopsies showed atherosclerosis only. CT scan of the head February 26, 1992, was negative. An enhanced cranial MR scan on April 9, 1992, demonstrated a right cavernous sinus mass with decreased T1 and increased T2 signal intensity with uniform contrast enhancement. There was also thickening and contrast enhancement of the meninges of the right middle cranial fossa (Fig. 1A). CSF studies showed three white cells, 53 red cells, protein 48 mg/dl, glucose 58 mg/dl, with cytology negative for malignant cells. Sinus biopsy on April 14, 1992, showed "chronic inflammatory changes without vasculitis or granuloma" and mycobacterium was suspected, as the patient stated that his mother had tuberculosis. The patient was started on INH and rifampin and, later, because his clinical status was unchanged, on steroids.

The patient was seen at the Mayo Clinic Jacksonville initially on July 14, 1992. He felt that his neurologic status had been stable since being on the steroids. He denied any eye pain, diplopia, tinnitus, dysphagia, dysarthria, or other neurologic complaints except for occasional mild bifrontal headaches.

General neurologic examination revealed a left peripheral incomplete cranial nerve VII palsy and bilateral sensorineural hearing loss (left greater than right). Acuity was 20/60 OD and NLP OS with a 4+ relative afferent pupillary defect on the left. The left eye was mildly exotropic and hypertropic with decreased movement in all planes. Visual fields in the right eye were normal. The right funduscopic examination was normal, but the left disc was pale with attenuated vessels. The remainder of the neurologic examination was normal.

No gammopathy was detected on serum immunoelectrophoresis or protein electrophoresis studies. Sedimentation rate was 41 mm with hemoglobin 12.2, hematocrit 36.7, MCV 95.2, and white count 7,000. Chemistries were normal with normal ACE (12.5 U/L); thyroid stimulating hormone, B12, and folate levels; ANCA; and RPR. Spinal tap revealed an opening pressure of 195 mm of water with seven white cells (91% lymphs, 1% polys, 8% monocytes); five red blood cells; protein, 38.3 mg/dl; glucose, 62 mg/dl; cryptococcal antigen, negative; VDRL, negative; fungal, AFB, bacterial stains and cultures, negative; cytology, atypical lymphocytes (with multiple small nucleoli) with reactive monocytosis; immunostaining of spinal fluid cells and B-cell stains were negative with T-cell stains weakly positive. Too few cells were present for gene rearrangement studies by Southern methodology.

FIG. 1. Axial (A) and coronal (B) enhanced magnetic resonance scans showing enhancing right cavernous sinus mass (arrow) and thickened enhancing meninges of the right middle cranial fossa (arrowhead).
The enhanced cranial MR scan of June 2, 1992, showed no change in the enhancing cavernous sinus mass or meningeal enhancement. New enhancing soft tissue was seen in the left orbital apex with lateral displacement of the left optic nerve; there was also enhancement of the left optic nerve (Fig. 2A and B). No parenchymal lesions were present. Four-vessel cerebral angiography was negative.

A right temporal craniectomy and meningeal biopsy revealed atypical angiocentric granulomatous lymphoid infiltrates without associated necrosis, giant cells, or granuloma formation (Figs. 3 and 4). Immunostaining of the lymphoid infiltrates showed scattered CD3+ lymphocytes. The morphologic differential diagnosis was a vasculitis with an atypical lymphoid component versus angiocentric T-cell lymphoma. As tissues were fixed in formalin and the biopsy fragments were small, PCR-based T-cell receptor (TCR) gene rearrangement analysis was performed on paraffin section (6–8). A TCR gamma rearrangement was detected (Fig. 5). The combination of morphologic and T-cell receptor gene rearrangement findings was diagnostic of an angiocentric T-cell lymphoma, pleomorphic medium-sized, and large-cell T-cell lymphoma in the Kiel classification.

The patient was continued on steroids; later, cyclophosphamide was added. Six months after his presentation to Mayo Clinic Jacksonville, his neurologic status has remained unchanged.

**DISCUSSION**

The patient’s clinical picture was that of multiple cranial nerve palsies, involving the left optic nerve, left facial nerve, left ocular motor nerves, and bilateral acoustic nerves with systemic symptoms of low-grade fever, night sweats, and arthralgias. The left visual loss, normal initial funduscopic examination, and initial presence of a relative afferent pupillary defect all suggested a retrobulbar optic neuropathy. Although this optic neuropathy may have been caused by optic nerve compression in the orbital apex or optic canal, the rather acute onset of visual loss raised the possibility of a retrobulbar ischemic optic neuropathy. The multiple other cranial nerve palsies and MRI features suggested a diffuse, meningeal process. The clinically evident predominance of cranial nerve findings was on the left, while MRI studies revealed significant changes around the right cavernous sinus and right middle cranial fossa meninges. The finding of thickened enhancing meninges is nonspecific. The differential diagnosis in this patient primarily included inflammation, infection, and neoplasm, both primary and metastatic. Specifically considered were granulomatous etiologies such as tuberculosis, fungus, and sarcoid; bacterial etiologies; syphilis; histiocytosis X; lymphoma; carcinomatous meningitis; and idiopathic cranial pachymeningitis. A right temporal cranietomy and meningeal biopsy revealed angiocentric T-cell lymphoma.
Neurologic manifestations occur in approximately 30% of patients with angiocentric T-cell lymphoma (lymphomatoid granulomatosis) and are the presenting feature of the disease in up to 21% (4). The central nervous system clinical presentations include mass lesions with focal neurologic deficits and signs of increased intracranial pressure, multiple cranial nerve palsies, "aseptic meningitis," dementia and obtundation, and even extrapyramidal dysfunction (2). Kleinschmidt-DeMasters et al. noted that while pulmonary involvement is generally the most prominent finding in cases with CNS involvement, patients may present with early or dramatic CNS disease (2).

The radiographic presentations of CNS angiocentric T-cell lymphoma (lymphomatoid granulomatosis) are also variable (9-12). Most often reported are intraparenchymal lesions, which may be unifocal or multifocal, supra- or infratentorial in location, with variable contrast enhancement. These lesions may be solid or necrotic, commonly demonstrate hemorrhage, and may have associated leptomeningeal thickening and/or enhancement. Less often seen are cerebral infarction, ex-

FIG. 3. Granulomatous lymphoid infiltrate of meninges. H&E, x200.

FIG. 4. Angiocentric atypical lymphoid infiltrate (dark convoluted cells, upper arrow) admixed with endothelial cells of blood vessels (lower arrow). H&E stain, x400.
The retrobulbar optic neuropathy in our patient could have been secondary to optic nerve compression or ischemic retrobulbar optic nerve insult. Progressive visual loss associated with evidence of optic nerve dysfunction may be the presenting symptom in patients with B-cell lymphoma (23,24), and in some cases the optic disc on the affected side appears normal and a diagnosis of retrobulbar neuritis is assumed until visual loss progresses or until other neurologic signs and symptoms develop (25,26).

Thus, in patients with an optic neuropathy and multiple cranial nerve palsies, angiocentric T-cell lymphoma must be considered in the differential diagnosis of a diffuse meningeal process.

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T-CELL LYMPHOMA PRESENTATION

Magnetic Resonance Imaging of the Brain in Nonarteritic Ischemic Optic Neuropathy

Anthony C. Arnold, M.D., Robert S. Hepler, M.D., D. Rex Hamilton, M.S., and Robert B. Lufkin, M.D.

We wished to determine whether the number of central nervous system (CNS) white matter lesions on magnetic resonance imaging (MRI) is increased in patients with nonarteritic ischemic optic neuropathy (NAION). T2-Weighted axial images of the brain in 13 patients with acute NAION and 16 age-matched controls were used to tabulate the number of subcortical and periventricular white matter lesions. Groups were compared by t test for means, the Wilcoxon-Mann-Whitney rank-sum test, and chi-square test for proportions with at least one lesion. The mean number of CNS white matter ischemic lesions in the NAION group was 4.0 (range 0-20) as compared to 1.4 (range 0-7) in the control group. The difference in these samples suggested a significant increase in NAION (p = 0.069, rank-sum test). The proportions of patients with at least one lesion were not significantly different (53.8% NAION vs. 56.3% controls). The data suggest an increased number of CNS white matter lesions in patients with NAION.

Key Words: Ischemic optic neuropathy—Magnetic resonance imaging—CNS white matter lesions.

Nonarteritic anterior ischemic optic neuropathy (NAION) is presumed to result in part from microvascular insufficiency in the optic nerve head (1) and is purportedly associated with increased risk of cerebrovascular and cardiovascular disease (2-4). Subcortical white matter lesions on magnetic resonance imaging (MRI) are frequently observed in scans of the elderly and in such instances are believed to reflect small vessel cerebrovascular disease (5). We compared MRI scans of the brain in patients with acute NAION with those of age-matched controls to determine whether the number of CNS white matter lesions is increased in patients with this disorder.

PATIENTS AND METHODS

MRI of the brain was performed in 13 patients with acute NAION examined at the Jules Stein Eye Institute from 1989 to 1994. All patients were aged ≥45 years, with recent (≤30 days) onset of monocular visual loss and the presence of an afferent pupillary defect, optic disc swelling, and visual field loss consistent with NAION. No patients had evidence of previous visual loss in the same eye, systemic symptoms suggestive of vasculitis (including temporal arteritis) or demyelinating disease, or Westergren sedimentation rate >40 mm/h. Eleven patients were men and two were women, with a mean age of 61.2 years (range 48-71 years). Eight patients (61.5%) were hypertensive, and one (7.6%) was diabetic. None had had previous stroke.

MRI scan was performed in seven patients with NAION on a 1.5-T superconductive unit (Signa, General Electric, Medical Systems Division, Milwaukee, WI, U.S.A.) and in six on an 0.3-Tesla permanent magnet unit (Fonar, Melville, NY, U.S.A.), both with a 256 × 192 matrix. T2-
Weighted [repetition time (TR) = 2,200 ms Signa, 3,000 ms Fonar, echo time (TE) = 80 ms Signa, 85 ms Fonar] axial images (5 mm thickness, 2.5-mm gaps) were evaluated for the number of subcortical and periventricular white matter lesions present (Fig. 1).

Sixteen control patients matched for age and incidence of systemic hypertension and diabetes, with no previously diagnosed central nervous system (CNS) disease and otherwise negative MRI scans, were used for comparison. Controls were selected on the basis of quality of images of the brain from 29 patients in the same population (ACA clinical practice) who underwent imaging at UCLA Medical Center from 1991 to 1994. Nine patients were men and seven were women, with a mean age of 62.8 years (range 48–81 years). Nine (56.3%) were hypertensive, and two (12.5%) were diabetic; none had had previous stroke. All studies were accomplished on the 1.5-Tesla superconductive unit (Signa) with the same imaging parameters as those selected for NAION patients. Similar analysis of white matter lesions was performed.

Patients with NAION were compared with controls for number of white matter lesions by Student's t test for means and the Wilcoxon-Mann-Whitney rank-sum test. Proportions of patients with at least one lesion were compared between groups by the chi-square test.

**RESULTS**

Patient data are summarized in Tables 1 and 2. The mean number of lesions in the NAION group was 4.0 (range 0–20, SD ± 5.97) as compared to 1.4 (range 0–7, SD ± 2.13) in the control group, suggesting but not statistically confirming an increase in the NAION group (p = 0.143, t test). Comparison by the Wilcoxon-Mann-Whitney rank-sum test was more suggestive of an increased number of lesions in NAION (p = 0.069). Seven (53.8%) of 13 patients with disease demonstrated at least one lesion, as compared to nine (56.3%) of 16 controls (p = 0.897, chi-square test), an insignificant difference.

**DISCUSSION**

T₂-Weighted MRI of the brain demonstrates subcortical and periventricular white matter lesions in a significant number of elderly patients with no known CNS disease (5). Patients with hypertension, diabetes, cardiovascular, and cerebrovascular disease have an increased incidence of such lesions, which are believed to represent focal perivascular ischemic demyelination and gliosis (6). The degree of involvement with these foci may be an index of cerebrovascular disease (5).

NAION has also been associated with vasculopathic risk factors (2–4) and presumably reflects microvascular disease of the optic nerve head (1).

Jay and Williamson (7) compared nine patients with NAION with 11 controls for the number of subcortical white matter lesions, finding an increased number in patients with disease and a suggestive but not statistically significant difference in means (3.2 lesions in NAION vs. 0.9 in controls, p = 0.08, t test). The proportion of control patients

**TABLE 1. Clinical profile and MRI findings in 13 patients with NAION**

<table>
<thead>
<tr>
<th>Patient/age (yr)/sex</th>
<th>HTN/DM</th>
<th>No. of lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/64/M</td>
<td>+/-</td>
<td>0</td>
</tr>
<tr>
<td>2/52/F</td>
<td>+/-</td>
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</tr>
<tr>
<td>13/49/M</td>
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<td>1</td>
</tr>
</tbody>
</table>

MRI, magnetic resonance imaging; NAION, nonarteritic anterior ischemic optic neuropathy; HTN, hypertension; DM, diabetes mellitus.
TABLE 2. Clinical profile and MRI findings in 16 control patients

<table>
<thead>
<tr>
<th>Control/age (yr)/sex</th>
<th>HTN/DM</th>
<th>No. of lesions</th>
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</thead>
<tbody>
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</tr>
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<tr>
<td>15/63/F</td>
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</table>

MRI, magnetic resonance imaging; HTN, hypertension; DM, diabetes mellitus.

with hypertension, diabetes, or history of other cardiovascular or cerebrovascular disease was not reported.

We selected subjects in which comparable proportions of patients and controls demonstrated these risk factors to account for their effect on the number of white matter lesions. Analysis showed a similar increase in the number of lesions (mean 4.0 in NAION vs. 1.4 in controls). Because the data were considered nonparametric, we compared the groups by the Wilcoxon-Mann-Whitney rank-sum test in addition to the t test. The increased number of deep white matter lesions in NAION, significant at the p < 0.10 level, is further evidence that NAION occurs in the setting of diffuse small vessel disease, with CNS white matter abnormalities beyond those caused by vasculopathic risk factors such as hypertension and diabetes alone. Future studies directed at relating the number of such lesions to the incidence of subsequent contralateral NAION may indicate those patients at particular risk for its occurrence and thus most appropriately considered for potential prophylactic therapy.

The increase in number of lesions per subject was not carried through to the proportions with at least one lesion. We believe that this reflects the common occurrence of such abnormalities in all patients in this age group. Our control figures for the incidence of at least one lesion are significantly lower than the figure of 92% of Awad and associates (5) in patients aged >60 years. The difference most likely arises from patient selection; none of our patients or controls had evidence of other CNS disease, whereas those of Awad and associates (5) included patients with CNS tumors and previous irradiation, previous stroke, and hydrocephalus.

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REFERENCES

Optic Nerve Compression from a Basal Encephalocele

Gerard L. Herschewe, D.O., James J. Corbett, M.D., Karl C. Ossoinig, M.D., and H. Stanley Thompson, M.D.

A woman developed headaches, transient visual obscurations, anosmia, and decreased visual acuity. Ocular examination showed bilateral pulsatile proptosis and disc edema with choroidal folds. Standardized ophtalmic echography showed absence of bony orbital roofs, prominent dural pulsations, direct apposition of brain parenchyma and orbital tissues, and echographic signs suggesting bilateral optic nerve compression. CT and MRI showed a large defect in the floor of the anterior cranial fossa. The cribiform plate, both orbital roofs, and sphenoid bones were displaced by a large basal encephalocele. Clinical improvement followed reconstruction of the anterior cranial fossa and decompression of both optic nerves.

Frontal basal encephaloceles are congenital malformations in which brain parenchyma herniates through a bony defect in the cribiform plate and sphenoid bone. These disorders may be associated with midline facial defects and anomalous optic discs (1). Basal encephaloceles may produce unilateral or bilateral proptosis and visual loss due to compressive optic neuropathy (2). We report a case with bilateral pulsatile proptosis and compressive optic neuropathy. Proptosis and visual acuity improved following reconstructive surgery.

CASE REPORT

A 35-year-old right-handed woman had a year-long history of intermittent headaches which she attributed to "sinus congestion." The constant discomfort across her forehead was aggravated by bending over. Her nose felt "plugged up," especially in the mornings. She had brief, transient monocular visual obscurations in her right eye lasting only seconds. On one occasion after she had been lying down, she stood up abruptly and became completely blind for about 10 s. During the preceding year, she had noticed intermittent bulging of her eyes. During the last two months she had developed progressive proptosis associated with worsening vision. She felt that she had lost her sense of smell, but she insisted that her ability to taste her food was unaffected.

Examination

During the initial examination, the patient's visual acuity was 20/40 OD and 20/30 OS. Color vision was only slightly impaired (9/14 AO color plates in each eye). Foveal flicker fusion was definitely impaired (RE 18 Hz, LE 20 Hz; the normal
The pupils were equal in size and reacted well to light. There was a small (0.3 log unit) relative afferent pupillary defect OD. Fundus examination showed moderate right disc swelling with choroidal folds, and slight left disc swelling with choroidal folds. There was bilateral pulsatile exophthalmos (Fig. 1) with Hertel readings of 24 mm OD and 25 mm OS (base 100). Horizontal versions were mildly restricted in both directions. Vertical gaze was normal. Goldmann visual fields showed bilateral superior arcuate scotomas with enlargement of the blind spot. Speech was fluent, and insight, judgment, and comprehension were all normal. She was unable to recognize the odor of oil of cloves or of peppermint. The remainder of the neurological examination was normal.

Axial and coronal T1-weighted MRI showed downward herniation of brain parenchyma through the base of the skull into both orbits (Fig. 2). The CT scan showed absence of the cribiform plate and superior orbital roof and only remnants of the lesser wing of the sphenoid. There was herniation of brain parenchyma through the floor of the anterior cranial fossa with lateral displacement of both optic nerves (Fig. 3).

Standardized A-scan and B-scan echography (3,4) showed the absence of the bony roof in both orbits, mostly between 10:00 and 2:00 o'clock OD, and from 10:00 to 1:30 o'clock OS (Fig. 4). Brain and dura were herniated through the bony defects and were lying on top of the thinned levator and superior rectus muscles, below the level of the superior orbital rims. All these structures had prominent pulse-synchronous movements visible in real-time echography. Both optic nerves were surrounded by excessive subarachnoid fluid in their most anterior portions (Fig. 5). Alternating right and left prolonged maximal horizontal gaze (so-called "optic nerve exercise") was kept up for at least 3 min (4), and during this time the sheath distension decreased only minimally. Normally, all the subarachnoid fluid surrounding the optic nerves is expressed from subarachnoid space during this maneuver. The fact that no fluid could be expressed from the optic nerve sheaths is an echographic sign suggesting severe optic nerve compression (4).

A bifrontal craniotomy disclosed that both orbital roofs were missing. The sphenoid wing was completely absent on the right side and a small
FIG. 4. Standardized echograms from the right superior orbit and the overlying brain of the patient. Top left: A-scan echogram obtained by placing the probe on the right globe behind the limbus at 6:00 and by aiming the sound beam superiorly into the brain tissues through the globe and the adjacent thin, high reflective, superior orbital soft tissues (thinned superior rectus and levator muscles, left arrow); the brain tissues have irregular acoustic structure with low reflectivity: low spikes from the brain matter and single higher spikes from the large surfaces and vessels (between the two arrows). Bottom left: A-scan echogram obtained by placing the probe on the upper lid at 12:00 and directing the beam through the upper lid and adjacent dura (high spikes on the left) into brain tissue (irregularly distributed, mostly low spikes throughout the rest of the echogram). Top right: B-scan echogram obtained by placing the probe on the globe across the 6:00 meridian behind the limbus and by aiming a "transverse" acoustic section (transverse to the 12:00 meridian) steeply up into the brain through the globe and superior orbit. The upper end of this B-scan echogram corresponds to the nasal end of this acoustic section. The arrows indicate the curved lines representing the inferior gyrate surfaces of the brain, which are separated from the dura by nonreflective subarachnoid fluid. The weak signals at the far right of the echogram are artifacts (reverberation signals). Bottom right: Longitudinal B-scan echogram obtained in a direction perpendicular to the top B-scan echogram by aligning the acoustic section along the 12:00 meridian from anteriorly (upper end of echogram) to posteriorly.

remnant of the sphenoid wing remained on the left. There was a herniation of the gyrus rectus through a large defect in the cribiform plate. Dexon mesh filled with methylacrylic was used to make a new floor for the anterior cranial fossa to keep the frontal lobes out of the orbits. Following surgery, the patient's headaches and pulsatile proptosis improved.

DISCUSSION

An encephalocele is a herniation of brain tissue through a defect in the bony coverings of the skull.
FIG. 5. Standardized echograms showing the images of the right optic nerve and its sheaths, which are distended with subarachnoid fluid. **Top left:** A-scan measurement of the maximum arachnoidal diameter (distance between the two arrows corresponding to 8.12 mm) with the patient looking straight ahead. Arrows point to electronic gates, which were placed over the peaks of the temporal (left in the echogram) and nasal (right in the echogram) arachnoidal spikes (corresponding to the arachnoid/liquid interface). These spikes had been maximized in height, indicating perpendicular sound beam incidence at these interfaces. Note the steep descent and ascent of these signals, indicating the smoothness of the arachnoidal surface. The low spikes between the arrows come from the optic nerve, which, in this section, was not reached by a perpendicular beam. **Bottom left:** A-scan measurement of the maximum arachnoidal diameter (7.07 mm) during maximal abduction of the right eye (30 degree test) showing only a minor decrease from the straight ahead measurement (presumably because the fluid was distributed over a longer distance within the stretched optic nerve sheaths). **Right:** Axial B-scan echograms obtained in two planes perpendicular to each other (transverse on top and longitudinal at bottom). The optic discs are visibly elevated due to the papilledema. The increased “sheathing sign,” the separation of optic nerve (pial) and sheath (arachnoidal) surfaces by the nonreflective fluid, is clearly noticeable. The bottom B-scan shows the “flying bat” configuration typical of such a condition: The head of the bat is represented by the elevated disc; the two wings correspond with the fluid-filled spaces beneath the arachnoidal/dural sheaths, which are more distended in their anterior portion as seen above and below the optic nerve pattern in this echogram.

The term cranial meningocele is reserved for the forms in which the herniated sac contains only the meninges and cerebrospinal fluid (5).

The incidence of encephaloceles varies from 0.3 to 0.7 cases/1,000 births and 16% are familial (6). According to the location of the bony defect, encephaloceles are broadly classified as calvarial, frontal, and basal (7). Basal encephaloceles have
been further subdivided into the following groups: transphenoidal, transethmoidal, sphenethmoidal, frontosphenoidal, and sphenoorbital (8).

In children, a basal herniation is not visible externally and may remain clinically undetected within the nasal cavity, the epipharynx, or the orbit. A soft tissue mass present in the nasal cavity can be misinterpreted as a nasal polyp (9). The herniated mass may enlarge and become symptomatic with crying, jugular compression, or aValsalva maneuver.

In adults, encephaloceles may be discovered during an investigation for hypothalamic dysfunction (diabetes insipidus, hypogonadism) or visual disturbance (optic atrophy, bitemporal hemianopia) (10,11). Bilateral pulsatile proptosis may result if the herniating mass extends into the orbit. The differential diagnosis of pulsatile exophthalmos includes neurofibromatosis (12), acquired carotid-cavernous fistula, congenital arteriovenous malformations, venous varicocele, encephalocele (13), and trauma (14). Orbital encephaloceles frequently cause unilateral exophthalmos (15,16).

Various optic nerve abnormalities have been reported associated with basal encephaloceles, including pale discs, colobomas of the nerve head, optic disc pits (17), morning glory disc (18), and megalopapilla and other disc anomalies (19). The presence of such optic nerve anomalies, coupled with midline facial defects such as ocular hypertelorism and median cleft lip, should alert the clinician to suspect the presence of a basal encephalocele (11).

CT will define the bony abnormalities, although MRI provides more detailed assessment of associated brain anomalies, aberrant vascular structures, and occipital encephaloceles (20,21). In this case, standardized echography (3,4), besides showing the missing orbital roof and the real-time pulsations of the dura and adjacent tissues, helped to underline the optic nerve compression.

Unilateral visual loss due to optic nerve compression without associated midline facial defects and without pulsatile proptosis has been reported in one case (2). The patient, a 23-year-old male, had sudden loss of vision OD, a soft tissue density in the right ethmoidal sinus, and a bony defect in the cribriform plate that was surgically repaired. Following surgery, the visual acuity recovered from 20/70 to 20/30 and the visual field improved. Clinical suspicion of a basal encephalocele may be confirmed by a variety of imaging techniques, and these images are an essential part of a preoperative evaluation.

Acknowledgments: We would like to thank Dr. Behrouz Rassekh for providing the clinical details of this patient's operative and postoperative course.

REFERENCES

Acetylcholine Receptor Antibodies in Patients with Graves’ Ophthalmopathy

Daniel M. Jacobson, M.D.

Abstract:

Objectives: To determine the frequency and clinical correlates of acetylcholine receptor (AChR) antibody seropositivity in patients with Graves’ ophthalmopathy.

Materials and Methods: Fifty consecutive new patients with Graves’ ophthalmopathy diagnosed in an outpatient neuro-ophthalmology practice underwent determination of AChR-binding antibodies. Clinical and biochemical thyroid variables were compared between seropositive and seronegative patients. Clinical variables included age, sex, thyroid disorder, and duration and course of illness. Biochemical variables included thyroid hormone levels and thyroid antibodies. Seropositive patients were followed clinically to identify signs of myasthenia gravis.

Results: Four of 50 (8%) patients had definitely elevated levels of AChR-binding antibodies. No obvious differences existed between the seropositive and seronegative groups in regards to age, sex, underlying thyroid disorder, biochemical thyroid state, presence of thyroid antibodies, or duration and course of their disease. None of the four seropositive patients developed signs of myasthenia gravis during the median follow-up period of 4.5 years.

Conclusion: AChR-binding antibody seropositivity occurs in a small proportion of patients with Graves’ ophthalmopathy but, by itself, does not necessarily identify an individual with concurrent myasthenia gravis or an individual at risk to develop myasthenia gravis.

Key Words: Myasthenia gravis—Graves’ ophthalmopathy—Ophthalmoplegia—Acetylcholine receptor antibody—Autoimmune.
of orbitopathy into one of three groups: stable, active, and chronic. Briefly, stable disease implied that no change in signs and no active chemosis or orbital congestion was observed for at least six months. Active disease implied that increasing proptosis, restrictive ophthalmoplegia, chemosis, or orbital congestion was observed within six months. Patients who developed compressive optic neuropathy were also categorized as having active disease. In general, patients with active disease usually had external evidence of orbital congestion and had physical findings whose progressive changes were readily apparent over the course of a few weeks to two months. Chronic disease implied that changes in proptosis, ophthalmoplegia, and external signs of orbital congestion were observed but were much milder and developed much slower than those signs observed with active disease. In general, patients with chronic disease had mild or no chemosis or soft tissue congestion and had physical findings whose changes were apparent only with prolonged comparison between follow-up evaluations of no less than six months.

The biochemical state of thyroid function was determined at the time Graves' ophthalmopathy was diagnosed by assessing levels of thyroid hormones, including total thyroxine (Emit Assay; Syva Co., Palo Alto, CA, U.S.A.) and a supersensitive assay for thyrotropin (Bio-Rad CoTube Assay; Bio-Rad Laboratories, Hercules, CA, U.S.A.), as suggested by the American Thyroid Association's guidelines for use of laboratory tests in thyroid disorders (8). While it is recognized that performing thyrotropin-releasing-hormone stimulation assays may be more sensitive for detecting subclinical hyperthyroidism in patients with Graves' ophthalmopathy and normal baseline thyroid hormone levels, this test was not routinely performed on all patients. In addition, patients underwent determinations of microsomal antibodies and thyroglobulin antibodies using a commercially available microagglutination assay (Sera-Tek; Miles, Inc., Elkhart, IN, U.S.A.). Normal titers are ≤1:100.

AChR-binding antibody levels were determined by an immunoprecipitation assay using AChR complexed with radioactively labeled α-bungarotoxin (9,10). All samples were submitted to the Neuroimmunology Laboratory, Mayo Clinic (Rochester, MN, U.S.A.) for analysis, where normal values are ≤0.03 nmol/L. A case control design was felt to be unnecessary since the patients in this study underwent the exact assay performed by Lennon and Howard (9), who found that values of AChR-binding antibody were 0.03 nmol/L or less in all of their 48 normal control subjects. Furthermore, false positive results using this assay in neurological control subjects are rare and only occurred in two of 22 subjects with amyotrophic lateral sclerosis (0.11 and 0.12 nmol/L), and one of 17 subjects with unexplained ptosis unassociated with myasthenia gravis whose AChR-binding antibody level was only 0.04 nmol/L (10).

RESULTS

Six patients with Graves' ophthalmopathy had levels of AChR-binding antibodies above the 0.03 nmol/L cut off. However, the level of seropositivity in two of these patients was so low (0.04 nmol/L) that they were considered insignificant. The levels in three of the remaining four seropositive patients (Table 1) were elevated within the low end of the range typically observed in patients with generalized myasthenia gravis (9,10). The value in a fourth seropositive patient (Table 1, patient 3) was markedly elevated. Accordingly, the frequency of definite AChR-binding antibody seropositivity in this population of Graves' ophthalmopathy was four of 50 (8%) patients. The number of seropositive patients was too small to apply meaningful statistical comparisons between the seropositive and seronegative groups. However, there were no obvious differences between these two groups of patients in regards to their age, sex, and underlying thyroid disorders (Table 2). Likewise, the clinical and laboratory correlates of the seropositive and seronegative groups with Graves' ophthalmopathy were similar (Table 3).

<table>
<thead>
<tr>
<th>Pt./age (yr)/sex</th>
<th>Thyroid disorder</th>
<th>Current thyroid state</th>
<th>AChR-binding antibody (nmol/L)</th>
<th>Microsomal antibody titer</th>
<th>Thyroglobulin antibody titer</th>
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<td>Euthyroid</td>
<td>7.96</td>
<td>1:200,000</td>
<td>1:102,400</td>
</tr>
<tr>
<td>4/8/1F</td>
<td>Diffuse toxic goiter</td>
<td>Euthyroid</td>
<td>0.21</td>
<td>&lt;1:100</td>
<td>&lt;1:100</td>
</tr>
</tbody>
</table>
None of the seropositive patients were receiving penicillamine, had relatives with myasthenia gravis, or had tardive dyskinesia, primary biliary cirrhosis, or known thymic tumors, other conditions that have been associated with elevated levels of anti-AChR (11). None of the four seropositive patients had other autoimmune disorders at the time of diagnosis or during the follow-up period. Anti-nuclear antibody assays were performed in three seropositive patients (patients 1, 3, and 4) and were negative in all three. All four seropositive patients were followed to identify any clinical features of myasthenia gravis. The follow-up period ranged from two and one half to five years (median, four and one half years).

Patient 1 (Table 1) developed mild proptosis and redness of both eyes at the same time she developed thyrotoxicosis seven years before her evaluation. She was treated with radioactive iodine and subsequently required thyroid replacement for iatrogenic hypothyroidism. Her orbital symptoms remained stable during the next seven years. She had mild bilateral proptosis, lid retraction, and lid lag, but no signs of ocular or generalized myasthenia gravis. She has been followed for two and one half years without any progression of Graves' ophthalmopathy and without any signs of myasthenia gravis.

Patient 2 (Table 1) experienced proptosis of her left eye for the preceding four months. She developed thyrotoxicosis two years earlier, which was treated with radioactive iodine. She then required thyroid replacement for iatrogenic hypothyroidism. One year prior to recognition of her thyroid disorder she experienced vertical diplopia which has since remained stable. A repetitive nerve stimulation study was normal at the time she presented with diplopia. She had a small inconstant vertical ophthalmoplegia, mild bilateral lid retraction, and mild proptosis of her left eye. Orbital

### TABLE 3. Summary of clinical and laboratory correlates of Graves' ophthalmopathy

<table>
<thead>
<tr>
<th>Years present</th>
<th>Total group</th>
<th>AChR-seropositive group</th>
<th>AChR-seronegative group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>1 wk–25 yr</td>
<td>0.5–7 yr</td>
<td>1 wk–25 yr</td>
</tr>
<tr>
<td>Median</td>
<td>1 yr</td>
<td>3 yr</td>
<td>0.9 yr</td>
</tr>
<tr>
<td>No. Unknown</td>
<td>11</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Current thyroid state (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Euthyroid</td>
<td>33</td>
<td>2</td>
<td>31</td>
</tr>
<tr>
<td>Hyperthyroid</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Hypothyroid</td>
<td>13</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Thyroid antibody positive (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microsomal</td>
<td>18</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>Thyroglobulin</td>
<td>6</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Course</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable</td>
<td>37</td>
<td>3</td>
<td>34</td>
</tr>
<tr>
<td>Active</td>
<td>16</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Chronic</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

### TABLE 2. Clinical characteristics of patients with Graves' ophthalmopathy

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Total group (n = 50)</th>
<th>AChR-seropositive group (n = 4)</th>
<th>AChR-seronegative group (n = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>23–79</td>
<td>29–67</td>
<td>23–79</td>
</tr>
<tr>
<td>Median</td>
<td>56</td>
<td>51</td>
<td>56</td>
</tr>
<tr>
<td>Sex (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>38</td>
<td>3</td>
<td>35</td>
</tr>
<tr>
<td>Male</td>
<td>12</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Thyroid disorder (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse toxic goiter</td>
<td>19</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>Primary hypothyroidism</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Nontoxic (euthyroid) goiter</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Benign (nonfunctioning) nodule</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Subacute thyroiditis (hypothyroid)</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Chronic lymphocytic thyroiditis (hyperthyroid)</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>None/euthyroid</td>
<td>21</td>
<td>1</td>
<td>20</td>
</tr>
</tbody>
</table>
computed tomography confirmed enlargement of the extraocular muscles of both orbits in a pattern consistent with Graves' ophthalmopathy. Her orbitopathy has remained stable during the subsequent four and one half years. She has not developed any clinical signs of myasthenia gravis. A plain chest radiograph obtained one year following her initial evaluation did not show a mediastinal mass.

Patient 3 (Table 1) noted "ptosis" of his left upper eyelid for the preceding six months. His examination revealed normal position of the left upper eyelid, mild retraction and lag of the right upper eyelid, minimal injection around the horizontal rectus muscle insertion sites, and minimal proptosis of the right eye. He had no signs of myasthenia gravis. Orbital computed tomography showed mild enlargement of the medial and inferior rectus muscles of both orbits. When his AChR-binding antibody titer returned markedly elevated (Table 1), the possibility of superimposed ocular myasthenia was entertained as a cause for his eyelid asymmetry. Intravenous injection of edrophonium did not change the resting position of the left eyelid. Single-fiber electromyography was normal. Antibody determination at a different laboratory also returned markedly elevated at 7.4 nmol/L (normal range, less than 0.8 nmol/L). Assay for anti-striated muscle antibody was negative. He has been followed for four and one half years without any progression of Graves' ophthalmopathy and without any signs of myasthenia gravis.

Patient 4 (Table 1) developed thyrotoxicosis and was treated with radioactive iodine five years before her evaluation. She then required thyroid replacement for iatrogenic hypothyroidism. She experienced vertical diplopia and nonfluctuating mild ptosis of her left upper eyelid three years before her evaluation. Her examination revealed mild bilateral restrictive ophthalmoplegia, mild right eyelid retraction and lag, mild nonfatigable left upper eyelid ptosis, and mild proptosis of the left eye. Computed tomography confirmed thick extraocular muscles in both orbits in a pattern consistent with Graves' ophthalmopathy. She had no other symptoms or findings of myasthenia gravis. In addition to her elevated AChR-binding antibody level (Table 1), she also had an abnormal AChR-modulating antibody assay of 64% (normal values, 0-20%), but a normal AChR-blocking antibody assay of 1% (normal values, 0-25%). The course of her orbitopathy was characterized by progressive restriction of ocular motility, increasing nonfatigable ptosis and levator function impairment of the left upper eyelid, and progressive proptosis. A follow-up AChR-binding antibody level three and one half years after the initial determination remained elevated at 0.13 nmol/L. During this period of time, two intravenous edrophonium tests produced no improvement of her ptotic left upper eyelid or ophthalmoplegia. Single-fiber electromyography and repetitive nerve stimulation studies were normal. Four and one half years after her initial evaluation, she developed left-sided compressive optic neuropathy treated with corticosteroids and then orbital decompressive surgery. The ptosis of her left eyelid did not improve during the six-week period that she received corticosteroids. She never developed other signs of myasthenia gravis. The progressive left upper eyelid ptosis and levator impairment was thought to result from mechanical compression of the levator palpebrae by her massively enlarged superior rectus muscle. Annual plain chest radiographs failed to identify a mediastinal mass.

DISCUSSION

This study confirms that AChR-binding antibody seropositivity occurs in a small proportion of individuals with Graves' ophthalmopathy. Because of the low frequency of false seropositivity, and the low concentration of AChR-binding antibody in three of the four seropositive patients identified, one must consider whether seropositivity occurs in patients with Graves' ophthalmopathy simply because of a failure of the assay's specificity, or occurs because of some specific immunological relationship between Graves' ophthalmopathy and myasthenia gravis. Unfortunately, this study was not designed to specifically address this issue.

Few other studies have tried to address the issue of AChR antibody seropositivity and Graves' ophthalmopathy. Robb et al. (4) identified three of 40 (7.5%) elderly patients with thyroid antibodies who had elevated AChR antibody levels using a similar assay technique. However, these investigators did not report whether their patients with thyroid antibodies had other laboratory or clinical features of thyroid disease or Graves' ophthalmopathy. Howard et al. (10) failed to identify AChR-binding seropositivity in 84 patients with Graves' thyroid disease; the presence of orbitopathy was not mentioned in this report.

Tanaka and Miyatake (12) found elevated levels of AChR antibodies in nine of 50 (18%) Japanese individuals older than 70 years of age. They suggested that false-positive results may occur in elderly individuals on the basis of altered cell-
mediated immunity associated with aging (12). This association is unlikely to explain the seropositivity of the four patients described in this study since all were less than 70 years of age (range 29–67 years; median 51 years). In fact, the youngest patient in the study (patient three) had the highest AChR-binding antibody level. Robb et al. (4) were unable to confirm a relationship between increasing age and false-positive AChR antibody levels in Caucasians.

Other techniques to measure AChR antibodies using other assay systems exist (9,10) but were not routinely performed in this study. The AChR-blocking antibody assay, as described by Lennon and Howard (9), was designed to detect antibodies that react with the ACh binding region of the AChR. Such antibodies are not detectable in the AChR-binding assay because the neurotransmitter binding region of the AChR has such high affinity for α-bungarotoxin, the substrate used in the AChR-binding assay. The AChR-blocking antibody assay is less sensitive than the assay employed in this study (10). The AChR-modulating antibody assay, also described by Lennon and Howard (9), was designed to assess the degree of degradation of the AChR that results from antibodies binding to multiple extracellular sites, a process that causes cross-linking and subsequent endocytosis of the AChR. The AChR-modulating antibody assay demonstrates a frequency of seropositivity in myasthenia gravis very similar to the AChR-binding antibody assay, but has the advantage of occasionally identifying patients with myasthenia gravis who are seronegative using the AChR-binding antibody assay (10). Accordingly, it is possible that the frequency of seropositivity identified in this study might have been higher had the AChR-modulating antibody assay been used instead of the AChR-binding antibody assay.

None of the four seropositive patients in this study developed clinical signs of myasthenia gravis during their median follow-up period of four and one half years. Electrodiagnostic assessment of neuromuscular transmission performed in three of the seropositive patients (patients 2-4) failed to provide evidence for subclinical myasthenic involvement. AChR-binding antibody seropositivity occurs in a small proportion of patients with Graves' ophthalmopathy but, by itself, does not necessarily identify an individual with concurrent myasthenia gravis or an individual at risk to develop myasthenia gravis. The diagnosis of suspected superimposed ocular or generalized myasthenia gravis in a patient with Graves' ophthalmopathy requires confirmation by means other than the detection of AChR-binding antibody seropositivity.

REFERENCES

Optic Neuropathy, Headache, and Diplopia with MRI Suggestive of Cerebral Arteritis in Relapsing Polychondritis

Guy G. Massry, M.D., Sophia M. Chung, M.D., and John B. Selhorst, M.D.

The pathogenesis of central nervous system disease in relapsing polychondritis (RPC) is unknown but may be related to cerebral arteritis. Previous reports have described clinical and histopathologic evidence of cerebral vasculitis in RPC; however, a neuroimaging correlate has not been reported. We present a 36-year-old man with neuro-ophthalmic features of RPC whose magnetic resonance imaging revealed multifocal gray- and white-matter high intensities. This pattern is consistent with cerebral arteritis as described in other systemic vasculitides.

Key Words: Relapsing polychondritis—Vasculitis—Magnetic resonance imaging.

In 1923 (1), Jaksch-Wartenhorst first described the disease we know today as relapsing polychondritis (RPC). He called it "polychondropathia." In the ensuing years, the disorder was referred to as systematic chondromalacia (2) and chronic atrophic polychondritis (3). It was not until 1960 that the name RPC was introduced by Pearson, Kline, and Newcomer (2).

RPC is characterized by recurrent episodes of inflammation involving various cartilaginous and connective tissue structures throughout the body (1). The characteristic clinical manifestations include auricular, nasal, and laryngotraheal chondritis, polyarthritis, and inflammation of the eye and inner ear (1,2).

Ocular manifestations occur in ~60% of cases and commonly include episcleritis, scleritis, iritis, conjunctivitis, and keratitis (4). Neurologic complications have been considered rare (5) or have attracted little attention (6), and their pathogenesis is unclear. Consequently, neuro-ophthalmic manifestations of RPC such as diplopia (5,7,8-10) and optic neuropathy (5,7,8,11-15) have been described less frequently than other ocular manifestations (4).

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Although clinical evidence of cerebral vasculitis in RPC has previously been inferred (1,16), only recently has histopathologic documentation of cerebral vasculitis been reported in association with RPC (6). Magnetic resonance imaging (MRI) consistent with cerebral arteritis has been described in a number of systemic vasculitides (17); however, no such correlation has been established with RPC. We describe a patient with ophthalmic and neuro-ophthalmic features of RPC, whose MRI is consistent with cerebral vasculitis.
CASE REPORT

A 36-year-old man complained of 1 year of intermittent pain, swelling, and hyperemia of both ears, bitemporal headaches, red eyes, tinnitus, and horizontal diplopia. He also described episodes of malaise, nasal congestion, and occasional joint pain. By dieting, he had lost 70 lb over the previous year. Laboratory studies included a normal CBC and chemistry panel with a nonreactive rheumatoid factor, anti-nuclear antibody, and HLA-B27. Erythrocyte sedimentation rate (ESR) was 30 mm/h. Lumbar puncture revealed only a mildly elevated protein of 85 mg/dl with an opening pressure of 210 mm of clear fluid, five lymphocytes, a glucose of 52 mg/dl, and no oligoclonal bands. An electroencephalogram (EEG) revealed diffuse slowing with an intermittent delta rhythm. A brainstem auditory evoked response (BAER) was normal, but visually evoked potentials (VEP) were bilaterally delayed. A computed tomogram of the brain was normal. MRI demonstrated a number of hyperintensities in the basal ganglia bilaterally (Fig. 1, left). Addition of gadolinium enhanced smaller adjacent areas, an area in the left posterior thalamus, and also a wedge-shaped area in the cortical gray matter (Fig. 1, right).

The patient was treated with a short course of oral prednisone (20-mg taper over 2 weeks), and all of the symptoms except his red eyes resolved. He had been off steroids for 3 months when he was referred for evaluation.

On examination, the patient was a 6 ft 2 in, 270 lb, right-handed man. Visual acuity measured 20/15 in both eyes. Pupils were 6 mm in the dark, with good light and near reactions, and no afferent pupillary defect. Ocular motility was full. Slit-lamp examination demonstrated 1+ conjunctival hyperemia, greater nasally in both eyes. There was also a focus of nodular episcleritis at 4 o'clock near the limbus of the right eye (Fig. 2). There was no evidence of iritis or vitreitis. Intraocular pressure was 10 mm Hg in both eyes. The fundus demonstrated mild disc edema, greater on the left than the right (Fig. 3), with a normal macula, vessels, and peripheral retina. Goldmann visual fields were full, and color testing was normal. External examination demonstrated hyperemic, thickened earlobes bilaterally, with loss of the normal curvilinear definition of the helix and antihelix (Fig. 4, left). General neurologic examination was normal.

A biopsy of the right earlobe revealed focal necrosis of cartilage, with an associated inflammatory response, and pleomorphic chondrocytes devoid of their normal polarity (linear arrangement) (Fig. 4, right). A diagnosis of RPC was made. An echocardiogram and pulmonary function tests were within normal limits. Oral prednisone, 30 mg a day, was initiated and was slowly tapered over 3 months to a dosage of 10 mg a day. Except for minimal ear swelling and tenderness, the examination is unchanged, and his neurologic symptoms have not recurred.

DISCUSSION

Diagnostic criteria for RPC were described by McAdam and colleagues. A definitive diagnosis is determined by the presence of three or more of the following clinical features: bilateral auricular chondritis, nonerosive seronegative inflammatory polyarthritis, nasal chondritis, ocular inflammation, respiratory tract chondritis, and cochlear or vestibular dysfunction or both (1). Histologic examination of involved tissue, revealing necrosis of cartilage, mononuclear cell infiltration, and disorganized chondrocyte maturation (1), confirmed the diagnosis. Our patient's findings of auricular pain, tenderness, and structural changes, ocular inflammation, and vestibular dysfunction (tinnitus), along with characteristic biopsy findings, established the diagnosis of RPC.

The commonest age of onset of RPC is between 40 and 60 years (4), and it occurs equally in both sexes without familial predisposition (1). Although the etiology of RPC is unknown, it appears related to immune-mediated injury in multiple tissues.

FIG. 1. Left: T-2 weighted magnetic resonance image demonstrates multiple zones of high intensity in the basal ganglia bilaterally. Right: Addition of gadolinium to a T-1 weighted image reveals multifocal small areas of enhancement in the right insular and contiguous regions. There is a similar lesion in the left posterior thalamus and a wedge-shaped enhancement within the gray matter of the right parieto-occipital cortex.
CEREBRAL ARTERITIS IN RELAPSING POLYCHONDRIITIS

There are no laboratory tests specific for RPC, with the only consistent finding being an elevated ESR during active disease (1). Consequently, its activity is monitored by serial ESR measurements.

The course of RPC is quite variable (7,16) but by no means is it a benign disorder. Michet et al. (16) reviewed 112 cases, of which 41 patients died. The 5- and 10-year probabilities for survival after diagnosis were 74 and 55%, respectively, with the most frequent causes of death being infection (12 cases) and systemic vasculitis (seven cases). Malignancy (five cases) was the most frequent cause of death unrelated to RPC.

The mainstay of therapy for patients with RPC is systemic corticosteroids, and most patients do well with this treatment (7). A trial of topical steroids for those patients with only mild to moderate ocular disease, such as episcleritis or anterior uveitis, may be attempted. However, these patients must be followed-up closely with a rheumatologist, with initiation of systemic therapy at the first signs of systemic flare-up.

Dapsone has also been reported to be effective in treating RPC (19,20). Less frequently, if systemic corticosteroids do not control the disease process, more potent immunosuppressive therapy, such as azathioprine, is required (7).

As previously mentioned, neurologic complications are rare in RPC (5). In reviewing 165 cases from the literature, Willis et al. (7) found that neurologic manifestations occur in the following decreasing order: diminished hearing, vertigo, headache, tinnitus, nystagmus, paresthesias, optic neuropathy, diplopia, and facial weakness. Sundarem and Rajput (5) reported that cranial nerve disorders are the most common neurologic complications, with involvement of the optic nerve being most common, followed by the sixth, seventh, and eighth cranial nerves. They also postulated that cerebral vasculitis was the underlying cause of neurologic disease, but they lacked neuropathologic confirmation. Other neurologic symptoms reported include hemiplegia, cerebellar dysfunction, seizures, confusion, and hallucinations (5,7).

In a combination of two previous reviews, systemic vasculitis occurred in ~18% of patients with RPC, of which 21% had clinical evidence consistent with central nervous system vasculitis (1,16). In 1988, Stewart et al. (6) demonstrated histopathologic documentation of cerebral vasculitis in a 32-year-old man with aseptic meningitis and RPC. A radiologic counterpart to this clinical and histopathologic data has not previously been documented.

In 1987, Miller et al. (17) reported that MRI was a sensitive method for detecting clinical or subclinical cerebral vasculitis in patients with systemic vasculitis. They scanned 24 patients with various forms of systemic vasculitis diagnosed by clinical and laboratory findings (10 with systemic lupus erythematosus, nine with Behçet's disease, two with polyarteritis nodosa, two with retinal vasculitis, and one with Cogan's syndrome). They identified the following: periventricular lesions (12 patients), lesions of the cerebral hemispheres discrete from the ventricles (nine patients), cerebellar lesions (two patients), wedges in the recognizable territory of a major cerebral artery (two patients), and brain stem lesions (one patient). No reference was made with regard to T1, T2, or gadolinium-enhanced images.

Our patient's MRI scan demonstrates multiple
FIG. 4. Left: A swollen and hyperemic auricle obscures the normal curvilinear definition of the helix and antihelix (arrows). Right: Right earlobe biopsy demonstrating liquefaction necrosis of cartilage (large arrow), infiltration of inflammatory cells (small arrows), and pleomorphic chondrocytes devoid of their normal polarity (linear arrangement) (above).

high-intensity lesions in the basal ganglia bilaterally (Fig. 1, left). Addition of gadolinium resulted in enhancement of small multifocal areas in the right insular region, one in the left posterior thalamus, and one in the right parieto-occipital cortex (Fig. 1, right). The latter is a wedge-shaped lesion that corresponds to the anatomic boundaries of the gyri and the distribution of cerebral small vasculature. This type of lesion is characteristic of infarction. The multifocal gray and white lesions present in our patient's MRI, some evident only by addition of contrast, are very suggestive of cerebral arteritis and are consistent with the previous report by Miller et al.

This case is an MRI correlate to the previous pathologic findings of Stewart and colleagues. Angiographic confirmation of cerebral arteritis was deferred in the presence of a normal general neurologic examination. However, the complaints of headaches and diplopia and the findings of mild optic disc edema, abnormal EEG and VEP, and an elevated cerebrospinal fluid protein indicate a definite intracranial pathologic process. Whether the cerebral vasculitis is a manifestation of RPC or a secondary immune-related disorder is unknown. A preceding or coexistent rheumatic or autoimmune disease is seen in ~25% of patients with RPC (18). We now have clinical, histopathologic, and radiographic evidence linking cerebral vasculitis and RPC.

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Bilateral Disc Edema in an Adolescent Girl

Gregory S. Kosmorsky, D.O., Robert E. Foster, M.D., and Brian D. Ellis, M.D.

A 15-year-old, 160-pound, Caucasian girl noted the sudden, painless onset of a "spot" in her left eye. She was evaluated by a neurologist who diagnosed "papilledema." MRI scanning of the head was normal. Lumbar puncture revealed an opening pressure of 200 mm H₂O with normal cerebrospinal fluid constituents. The patient denied vitamin use, antibiotic use, or liver ingestion. The diagnosis of pseudotumor cerebri was made, and she was referred to ophthalmology for further evaluation.

On eye examination, the visual acuities were 20/20 OD and 20/20 OS. There was no relative afferent pupillary defect. Humphrey visual field was normal OD. An enlarged blind spot was noted OS. Her fundus examination was remarkable for bilateral disc edema with unusual disc contours (Figs. 1 and 2). An intravenous fluorescein angiogram showed focal hyperfluorescence of both optic nerve heads in a lobular pattern (Figs. 3 and 4).

Examination of the patient's father was remark-
BILATERAL DISC EDEMA

FIG. 3. Late phase of the fluorescein angiogram of the right eye. Note the lobular staining patterns of the discs here and in Fig. 4.

FIG. 4. Early venous phase of the left eye. See Fig. 3.

FIG. 5. Fundus examination of the patient's father revealed a peripheral retinal capillary hemangioma.

able for a retinal capillary hemangioma characteristic of von Hippel-Lindau disease (Fig. 5).

COMMENT

von Hippel-Lindau disease is a phakomatosis characterized by autosomal dominant inheritance with variable penetrance. This familial cancer syndrome reflects loss of function of the 3p25-26 region (1). Penetrance is dependent on age, with the onset typically being in the second and third decade. While retinal angiomas is the most common presenting feature, other findings can include cerebellar and spinal hemangioblastomas, renal cell carcinomas, pheochromocytomas, and renal, epididymal, and pancreatic cysts. Cerebellar hemangioblastoma and renal cell carcinoma represent the most common causes of death (2).

Schindler and colleagues (3) described 65 patients with hemangiomas of the optic disc (10 cavernous, 55 capillary): 53% of the patients presented with visual loss, while 30% were found on routine eye examination. These retinal tumors may be either the endophytic type (most common) and grow toward the vitreous, or the exophytic type as seen in this case.

REFERENCES

Intracranial Hypertension and the Syndrome of Acquired Hyperopia with Choroidal Folds

Daniel M. Jacobson, M.D.

An idiopathic syndrome of acquired hyperopia with choroidal folds has been characterized. Orbital imaging correlates of this syndrome include flattening of the posterior globe and distention of the perioptic subarachnoid space. The mechanism responsible for the clinical and radiographic findings of this syndrome is undefined. Two patients with unusual presentations of papilledema are reported whose clinical and radiographic findings were otherwise identical to those described in the idiopathic syndrome of acquired hyperopia with choroidal folds. One patient had unilateral disc edema and bilateral choroidal folds. The other patient had bilateral choroidal folds observed 2 years before he developed papilledema in both eyes. Both patients had intracranial hypertension, idiopathic in the first, and related to severe chronic obstructive pulmonary disease and cor pulmonale in the second. A third patient is also described who had typical clinical and orbital imaging findings of idiopathic unilateral acquired hyperopia with choroidal folds. He was also found to have mild intracranial hypertension. Intracranial hypertension can cause acquired hyperopia and choroidal folds and may be the underlying mechanism in some patients with what appears to be idiopathic acquired hyperopia with choroidal folds.

Key Words: Hyperopia—Choroidal folds—Papilledema—Idiopathic intracranial hypertension—Pseudotumor cerebri.
CASE REPORTS

Case 1

A 28-year-old man was referred to evaluate “papilledema of the left eye.” For the preceding 6 months, he had noted vague trouble judging distances and a few brief spells of transient dimming of vision in his left eye, after bending over. He also noted an intermittent, mild, dull, left-sided retro-orbital ache for the preceding 18 months. He first sought care from his optometrist, who found that he had developed +0.75 and +1.00 diopters of hyperopia in his right and left eye, respectively, since his last examination 4 years earlier. “Papilledema” of his left disc was noted. A consulting neurologist then obtained normal complete blood counts, serum chemistries, erythrocyte sedimentation rate, antinuclear antibody, and visual evoked potentials. Brain computed tomography was reportedly “normal.” Lumbar puncture, performed with the patient fully relaxed, on his side, and with his legs extended, revealed an opening pressure of 210 mm cerebrospinal fluid, three leukocytes/microliter, protein 36 mg/dl, glucose 57 mg/dl, and negative microbiological and cytological studies. He was otherwise healthy, taking no medications, and had no other neurological or visual symptoms.

When evaluated 1 week later, he was not obese (weight, 177 pounds; height, 71 inches). His best corrected visual acuity was 20/20 +2 in his right eye and 20/25 in his left eye. Cycloplegic refraction was plano +1.50 × 90 in his right eye, and +2.00 +1.00 × 65 in his left eye. Color vision, assessed using pseudoisochromatic plates (Richmond Products, Boca Raton, FL, U.S.A.), was normal in both eyes. He had a small afferent pupillary defect in his left eye, neutralized with a 0.3 log unit neutral density filter held before the right eye during the swinging flashlight test. Goldmann perimetry revealed mild enlargement of the relative scotoma around the absolute blind spot in the right eye and moderate enlargement of the absolute and relative blind spot in the left eye. The size of the relative blind spot decreased in the left eye when tested with serial addition of plus sphere. Ophthalmoscopy of the right eye revealed a flat, normal-appearing optic disc, and subtle, horizontally oriented retinal folds extending from the disc to the fovea (Fig. 1). Ophthalmoscopy of the left eye revealed a peculiar elevation and whitish opacification of the immediate peripapillary nerve fiber layer, with little swelling of the disc itself (Fig. 2). Numerous retinal folds were observed extending from the disc in all directions, but mainly in the horizontal plane (Fig. 2). No spontaneous venous pulsations were observed in either eye. Fluorescein fundus angiography, performed several weeks later, confirmed that the retinal folds were choroidal in origin in both eyes and demonstrated late leakage and staining of dye at the left disc border and immediate peripapillary retina, but not within the disc itself (Fig. 3). A-scan echography revealed the following axial measurements in the right and left eye, respectively: cornea to sclera, 23.7 mm, 23.3 mm; cornea to retina, 22.5 mm, 21.8 mm; scleral thickness, 1.2 mm, 1.5 mm. The remainder of his ophthalmic and neurologic examinations were normal.
FIG. 3. Case 1. Fluorescein fundus angiogram of the posterior pole of the left eye obtained 5 min after injection of dye, showing staining of the immediate peripapillary retina but not of the optic disc itself. Note that the fluorescein dye appears to be accumulating deep to the retinal vessels, not within the peripapillary nerve fiber layer. Also note the alternating hypofluorescent and hyperfluorescent lines representing choroidal folds.

Review of his previously performed "normal" computed tomography study suggested thickening and tortuosity of the left optic nerve sheath complex and flattening of the left posterior globe. High-resolution orbital computed tomography and magnetic resonance imaging confirmed that the thickened optic nerve sheath complex was due to dilation of the perioptic subarachnoid fluid space with expansion of the optic nerve sheaths on both sides (Figs. 4 and 5). The posterior globes were thickened and flattened in the region of the optic nerve insertion (Figs. 4 and 5). These findings were present bilaterally but were more apparent on the left.

He received acetazolamide, 1,500 mg daily in divided doses, and was followed serially over the next 3 years. His transient visual obscurations and retroorbital ache resolved within weeks. His visual acuity gradually improved to 20/15 in both eyes. His refraction remained plano in the right eye but gradually changed to +1.25 sphere in his left eye. The peripapillary nerve fiber edema around the left disc slowly improved during the 10-month period after initiation of treatment, although mild nasal edema persisted (Fig. 6). The choroidal folds remained unchanged (Fig. 6). A-scan echography measurements of axial lengths, serially measured during the first 19 months, did not significantly change. Orbital magnetic resonance imaging, repeated 3 years after his initial evaluation, showed similar changes without any significant reduction in optic nerve sheath distention or posterior globe flattening.

Case 2.

A 48-year-old man was referred to evaluate "papilledema." He had been followed at my institution for routine eye care for the past 10 years...
ACQUIRED HYPEROPIA WITH CHOROIDAL FOLDS

FIG. 6. Case 1. Posterior pole of the left eye, showing resolution of most of the peripapillary nerve fiber edema but persistence of choroidal folds.

with previous stable refractive errors of plano +0.50 × 180 in both eyes. He was evaluated in July 1991 for conjunctivitis. He had no other visual or neurological symptoms but had developed hyperopia (+1.00 + 0.25 × 90) and retinal folds in both eyes (Fig. 7). His visual acuity was 20/30 in both eyes, and his discs were flat (Fig. 7). Fluorescein fundus angiography confirmed horizontally oriented choroidal folds extending from both optic discs but no leakage of dye from the discs (Fig. 8). Computed tomography was reported as "normal" at that time but, in retrospect, suggested distention of the optic nerve sheaths and flattening of both posterior globes at the site of optic nerve insertion. When evaluated 1 year later, he remained asymptomatic and had the same findings. When reevaluated 1 year later in August 1993, massive bilateral optic disc edema was noted for the first time. He admitted to mild intermittent headaches since the 1960s, which had not changed in character during the past 3 years. However, he had experienced frequent, daily, posturally induced, transient visual obscurations and subjective pulsatile intracranial noises for the preceding 3 months.

His past medical history was significant for severe tobacco-associated chronic obstructive pulmonary disease. A typical arterial blood gas on room air showed pH, 7.32; pCO₂, 74 mm Hg; and PO₂, 42 mm Hg. He also had severe right-sided heart failure with pulmonary hypertension and secondary polycythemia, with a typical hemogram showing hematocrit 65% and hemoglobin, 21.8 g/dl.

When evaluated 1 week later, he was not obese (weight, 185 pounds; height, 67 inches). His best corrected visual acuity was 20/20 −2 in his right eye and 20/20 in his left eye. Non-cycloplegic refraction was +1.50 sphere in his right eye and +1.75 sphere in his left eye. Color vision was normal in both eyes. Goldmann perimetry showed moderate enlargement of the relative blind spot in both eyes. Ophthalmoscopy revealed marked hyperemic swelling of both optic discs with numerous nerve fiber layer hemorrhages (Fig. 9). The retinal veins were mildly full and tortuous. Fluorescein fundus angiography revealed early leakage of dye from the optic discs and persistence of the previously documented choroidal folds in both.

FIG. 7. Case 2. Posterior pole of the left eye, showing retinal folds extending horizontally from a flat optic disc.

FIG. 8. Case 2. Fluorescein fundus angiogram of the posterior pole of the right eye obtained 1 min after injection of dye, showing alternating hypo- and hyperfluorescent lines representing choroidal folds. Note the absence of staining of the optic disc.

FIG. 9. Case 2. Ophthalmoscopy of the left eye showing marked hyperemic swelling of the optic disc with hemorrhages.
FIG. 9. Case 2. Posterior pole of the right eye, showing massive, fully developed papilledema.

eyes. There was mild delay in venous filling but no capillary dropout, microaneurysms, or arteriovenous or retinochoroidal shunt vessels. The remainder of his ophthalmic and neurologic examinations were normal.

Orbital computed tomography revealed prominent optic nerve sheath distention and flattening of the globe at the insertion of the optic nerves on both sides (Figs. 10 and 11). Brain sections showed no findings of dural sinus thrombosis but revealed changes consistent with intracranial hypertension, including blunting of cerebral sulci, small ventricles, and obliteration of basal cisterns. These brain findings were not present on his original study 2 years earlier. He refused to undergo lumbar puncture. He was treated with serial phlebotomies and

FIG. 10. Case 2. Orbital computed tomography image in the axial plane after contrast administration, showing distention of the optic nerve sheath from dilation of the subarachnoid space on the left. Also note the subtile thickening and flattening of the posterior globe on the left.

received a brief course of oral corticosteroids for exacerbation of his pulmonary disease. His papilledema dramatically improved during the next several months, but his choroidal folds persisted.

Case 3

An otherwise healthy 46-year-old man was referred to evaluate choroidal folds. During the preceding 9 months, he had noted progressive blur when reading. Removing his spectacles resulted in clear vision. He denied headache, retroorbital pain, scotomatous visual loss, diplopia, or pulsatile intracranial noises. His optometrist noted retinal folds in his left eye and referred him to a retinal consultant who performed fluorescein angiography. This confirmed horizontally oriented choroidal folds streaming across the posterior pole of the left eye, extending through the optic disc and fovea. No choroidal folds were seen in the right eye. There was no leakage of dye from either optic disc.

He was overweight (weight, 218 pounds; height, 66 inches) but had not experienced any recent weight gain. His 4-year-old spectacle correction was $-2.25 + 0.75 \times 149$ in his right eye and $-2.50 + 0.25 \times 55$ in his left eye. Manifest refraction without cycloplegia was $-2.25 + 0.75 \times 160$ in his right eye and $-0.25 + 0.50 \times 78$ in his left eye. His best corrected visual acuity was 20/20 +3 in his right eye and 20/50 ~2 in the left eye. Color vision was normal and symmetrical between both eyes. Goldmann perimetry showed mild enlargement of the relative blind spot and mild central depression of his left eye and normal findings in his right eye. He had a 0.2 log unit relative afferent pupillary defect on the left. Ophthalmoscopy revealed normal optic discs in both eyes but without spontaneous venous pulsations. The chorioretinal folds
were easily visible in the left eye (Fig. 12); none was seen on the right. A-scan echography revealed the following measurements in the right and left eye, respectively: cornea to sclera, 26.5 mm, 25.8 mm; cornea to retina, 25.0 mm, 24.7 mm. The remainder of his ophthalmic and neurologic examinations were normal.

Orbital computed tomography revealed optic nerve sheath distention and flattening and thickening of the posterior globe on the left (Fig. 13); the brain appeared normal. Lumbar puncture, performed with the patient fully relaxed, on his side, and with his legs extended, revealed an opening pressure of 240 mm cerebrospinal fluid; one leukocyte/microliter; protein, 38 mg/dl; glucose, 59 mg/dl; and negative microbiological and cytological studies.

**DISCUSSION**

These three patients shared the seminal clinical features common to those patients originally described by Kalina and Mills (8) with the idiopathic syndrome of acquired hyperopia with choroidal folds, including documented hyperopic shifts and choroidal folds. In addition, the orbital imaging findings demonstrated in my three patients were the same as those described in the idiopathic syndrome of acquired hyperopia with choroidal folds (9,10,12). Optic disc swelling has been observed in other cases of acquired hyperopia with choroidal folds described by Dailey and colleagues (9; cases 3-5) and Garrity and colleagues (12; cases 6 and 7).

All three patients reported herein had evidence of intracranial hypertension, idiopathic in Cases 1 and 3, and related to severe cor pulmonale, chronic obstructive pulmonary disease, and polycythemia in Case 2. The cerebrospinal fluid opening pressure in Cases 1 and 3, although not dramatically elevated, were higher than the usual range observed in nonobese, healthy, young adults (13) and were in the range often observed in many patients with established pseudotumor cerebri (13,14). Other reported patients with the syndrome of acquired hyperopia with choroidal folds have also been found to have elevated cerebrospinal fluid pressure, including Case 3 reported by Kalina and Mills (8) and Dailey and colleagues (9), the patient reported by Corbett and colleagues (11), and Cases 6 and 7 reported by Garrity and colleagues (12). However, none of the investigators reporting this finding discussed the possible significance of intracranial hypertension in their patients (8,9,11,12). In fact, an opening pressure of 320 mm during lumbar puncture of one such reported patients was dismissed as being unrelated (8) or an artifact of technique (9). Although Case 2 did not undergo lumbar puncture to document his cerebrospinal fluid pressure, he had medical conditions that can cause intracranial hypertension (15), he developed ophthalmoscopic and visual sensory findings compatible with papilledema, and his computed tomography changes of the brain were consistent with intracranial hypertension.

The orbital imaging changes observed in my three cases are not only the same as those others have described in the idiopathic syndrome of acquired hyperopia with choroidal folds (9,10,12) but also exactly what is observed in patients with idiopathic intracranial hypertension (16,17). With in-
tracranial hypertension, the elevated subarachnoid pressure is directly transmitted from the intracranial compartment to the intraorbital compartment through the perioptic subarachnoid space (18), resulting in distention of the optic nerve sheaths (16,17). Elevation of optic perineural pressure has two consequences. First, it causes stasis of axoplasmic flow through the optic nerve head, resulting in axonal swelling and ophthalmoscopically apparent disc edema (19). Second, the elevated intraosheath pressure can cause the subarachnoid compartment to act as a mass at the point of contact with the globe, resulting in axial length shortening and choroidal folds (20).

The anatomical and physiological factors that dictate to what extent either papilledema or axial length shortening and choroidal folds will develop in intracranial hypertension are undefined. Although choroidal folds are often observed in patients with idiopathic intracranial hypertension (21), the ophthalmoscopic hallmark of this disorder is papilledema. The right eye of Case 1, the initial presentation of both eyes of Case 2, and the left eye of Case 3 in this report exemplifies the unusual development of choroidal folds as the initial ophthalmoscopic manifestation of intracranial hypertension. Given the similar orbital imaging appearance in other cases of acquired hyperopia with choroidal folds (9,10,12), I suspect that many of these cases may also represent unusual presentations of idiopathic intracranial hypertension.

Certainly Cases 1 and 3 in this report are not typical examples of patients with idiopathic intracranial hypertension. Unlike most patients with this disorder (21), these two individuals were men without headaches, diplopia, or pulsatile intracranial noises. The peculiar-appearing peripapillary disc edema in Case 1 and choroidal folds in Case 3 were strictly unilateral. Unilateral, or highly asymmetric, papilledema has been well described in idiopathic intracranial hypertension (22-26). In fact, idiopathic intracranial hypertension may rarely occur without papilledema (27). It is not known why one optic disc is protected from the effects of intracranial hypertension in unilateral cases of papilledema, although anatomical and physiological factors of the optic nerve head are believed to be important (25,26).

The unusual ophthalmoscopic and fluorescein fundus angiographic appearance of the left optic disc in Case 1 deserves further comment. The region of nerve fiber edema and fluorescein dye leakage was peripapillary, not within the disc itself. The intermediary tissue of Kuhnt lies between the outer retinal layers and the prelaminar region of the optic nerve head, is composed of tight junctions, and prevents leakage of materials, such as fluorescein dye and exudates, from the anterior optic nerve head from reaching the peripapillary retina (28). Perhaps compression of the posterior globe by the pressure of the distended optic nerve sheath at its insertion somehow mechanically transformed this intermediary tissue into a leaky barrier.

The syndrome of acquired hyperopia with choroidal folds, just like the syndrome of pseudotumor cerebri (29), is probably a heterogeneous group of disorders. At least some cases of acquired hyperopia with choroidal folds represent unusual presentations of idiopathic intracranial hypertension or secondary pseudotumor cerebri syndromes. Patients with newly diagnosed acquired hyperopia with choroidal folds should undergo brain and orbital imaging to exclude structural intracranial and intraorbital causes and to seek the orbital neuroimaging correlates of intracranial hypertension. Evaluation of cerebrospinal fluid opening pressure and constituents in patients with symptoms or neuroimaging findings of intracranial hypertension also seems prudent. Measurement of intracranial pressure in all patients with acquired hyperopia with choroidal folds would provide further insight into the frequency of intracranial hypertension causing this syndrome.

Addendum: Six months after Case 2 was last seen at my institution, he received a second opinion through the courtesy of Leonard A. Levin, M.D., Ph.D. (Madison, WI). He underwent a lumbar puncture which revealed an opening pressure of 370 mm cerebrospinal fluid (with normal constituents) and a normal magnetic resonance imaging study of his brain.

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REFERENCES

ACQUIRED HYPEROPIA WITH CHOROIDAL FOLDS

Vasculature and Morphometry of the Optic Canal and Intracanalicular Optic Nerve

Ping-I Chou, M.D., Alfredo A. Sadun, M.D., Ph.D., and Hwa Lee, M.D.

Abstract:
Objectives: To study the bony structure of the optic canal and the vasculature of the intracanalicular optic nerve in human cadavers.

Materials and Methods: Gross and microscopic examinations were performed in 25 optic canals from 13 cadavers to study the pattern of vascular supply of the intracanalicular optic nerve. Neoprene latex was injected through the most proximal part of the ophthalmic artery in seven optic canals. The intracanalicular branches from the ophthalmic artery were carefully identified and quantified. Quantitative measurements of the canal length, canal thickness, canal transverse area, optic nerve transverse area, and subdural space were done for the other 18 canals by means of semiautomated morphometric analysis system. Each canal was divided into anterior, middle, and posterior parts for better visualization and measurement.

Results: The ophthalmic artery gives off three branches that supply the intracanalicular optic nerve: medial collateral branch, lateral collateral branch, and ventral branch. Each branch pierces the dura and then supplies the nerve through the pia mater. The middle medial wall was the thinnest bony part of the canal (0.31 ± 0.06 mm). The optic canal, optic nerve, and subdural space were done for the other 18 canals by means of semiautomated morphometric analysis system. Each canal was divided into anterior, middle, and posterior parts for better visualization and measurement.

Conclusions: The vasculature within the bony canal is extremely delicate. Due to the limitation of this space, even a tiny amount of blood or swelling of the nerve (21.69 mm³) may cause optic nerve compression. It appears that these vessels could easily be disrupted in closed head injury by a shearing or concussive force, leading to ischemic infarction of the optic nerve. Since the narrowest portion of the canal is in the middle portion, it is the middle part of the optic canal that is most critical in doing an optic canal decompression.

Key Words: Optic canal—Ophthalmic artery—Optic nerve trauma.

Traumatic optic neuropathy is a vision-threatening disorder. Several pathophysiologic mechanisms have been proposed, the most likely being a vascular disruption of the intracanalicular optic nerve produced by either a shearing or concussive force after blunt head trauma or direct compression from a bony fragment. Extracranial, microsurgical decompression of the optic canal has been demonstrated as a sometimes effective method in the treatment of traumatic optic neuropathy (1-4). Surgery of the optic canal region requires detailed knowledge of this area. In the present study, gross and microscopic dissections of the optic canal were performed to study the relationship between the optic canal structure and intracanalicular optic nerve vasculature.

MATERIALS AND METHODS

Twenty-five fresh optic canals, including nerves, were dissected completely en bloc from 13 human cadavers. All of the specimens were obtained from the Department of Medicine, University of Southern California, with the approval of the institutional review board. The specimen was placed immediately into heparin water (3,000 units heparin/ml) to prevent coagulation of blood within the vessels and to lyse the red cells. After carefully rinsing with running water, Neoprene latex (No. 571, Dupont Co.) was injected through the most
proximal part of the ophthalmic artery in seven optic canals. The injected specimen was then immersed in concentrated hydrochloric acid overnight to digest the surrounding tissues and delineate a detailed vascular tree. The intracanalicular branches from the ophthalmic artery were carefully identified and quantified.

Eighteen other optic canals were fixed in 2% paraformaldehyde-2% glutaraldehyde for 24 h immediately after dissection and then divided into anterior, middle, and posterior parts. Each specimen was paraffin embedded, sectioned, and stained with Masson trichrome. Under stereomicroscopy, measurements were made of the length and thickness of the optic canal, and the branching pattern of the ophthalmic artery was studied. The thickness, diameter, transverse area, and subdural space of the optic canals and nerves were also measured by means of a computer assisted semiautomated image analysis system (Fig. 1).

RESULTS

The ophthalmic artery derived from the internal carotid artery in all of the 25 canals studied. At the cranial end, the ophthalmic artery was located mainly on the inferior medial side and rotated to the inferior lateral side at the orbital end (Table 1). The ophthalmic artery was observed to contribute three small branches of vessels to supply the intracanalicular optic nerve: the medial collateral, lateral collateral, and ventral branches. Occasionally, one or even two of the branches would be missing, and double ventral branches were noted in one case. In the optic canal, the ophthalmic artery ran intradurally, then penetrated the dura and became epidural at the orbital end.

By means of Neoprene injection, each of these small branches could always be traced back to the ophthalmic artery. Instead of supplying the optic nerve directly, these branches first ran into the dura, in which they proliferated a capillary network that penetrated through the subdural space to the optic nerve. The vasculature within the optic canal was extremely delicate. In the dura, the blood vessels, including the ophthalmic artery, were mainly located in the inferior quadrant. These vessels entered the pia through an arachnoid plexus and then supplied the optic nerve by a capillary network surrounding the optic nerve. As the vessels came to the pia, they distributed themselves evenly around the nerve.

Our quantitative measurements showed that the thickness of the bony canal wall varied not only from medial to lateral, but also from the anterior (orbital) to posterior (cranial) end (Table 2). The thick anterior medial wall was formed by the sphenethmoidal junction. The thinnest wall was located in the middle segment on the medial side (0.31 ± 0.06 mm). The posterior superior wall was not a real bony wall, but a falciform ligament.
formed by a fold of the dura. The length of the optic canal varied also (Table 3). The medial wall was the longest and is formed by the posterior ethmoid sinus and anterior sphenoid sinus walls. The shortest wall was the lateral wall, and it is formed by the optic strut. At the orbital end, the optic canal opening was a vertical ovoid, the horizontal and vertical diameters being 4.34 mm and 5.59 mm, respectively. In the middle part, the canal was round, the diameter being 4.55 mm. At the cranial end, the optic canal was a horizontal ovoid, the horizontal and vertical diameters being 6.73 mm and 4.64 mm, respectively.

The relationships between canal transverse area, nerve transverse area, and subdural transverse area are listed in Table 4. The middle of the canal is the narrowest part, being only 16.22 ± 5.15 mm² in cross-sectional area. The canal opens up at both ends, and the nerve transverse area gradually increases from anterior to posterior. The subdural transverse areas were 1.68 ± 0.67 mm², 1.52 ± 0.10 mm², and 2.31 ± 0.36 mm² from anterior to posterior, with a mean subdural space of 1.84 mm². This space was occupied by the cerebral spinal fluid only. The area occupied by the meninges was excluded during measurement. These data, multiplied by the average length of the canal (11.79 mm), could be considered as the potential space for optic nerve edema or hemorrhage (21.69 mm³).

However, this was not a closed space. Both at the orbital end and the cranial end the intracanalicular subarachnoid space communicated freely with the intracranial subarachnoid space.

**DISCUSSION**

Francois first studied the vascularization of the optic nerve pathway by means of Neoprene injection (Latex 572), microangiography, and serial mi-

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<th>TABLE 2. Thickness of canal walls (millimeters) at different levels and positions</th>
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croscopic sections (5-7). He found that the optic nerve was supplied by capillaries from the pia mater throughout its length; these capillaries deriving from branches from the ophthalmic artery, anterior cerebral artery, internal carotid artery, lacrimal artery, middle meningeal artery, and long posterior ciliary arteries. For the intracanicular course, branches from the internal carotid, anterior cerebral, and anterior communicating artery also made contributions that formed the peripheral vascular supply to the optic nerve (5). The proximal ophthalmic artery gave off a central optic nerve artery that formed the axial nutritional system of the optic nerve (6,7). However, this scheme was later revised by Hayreh, who believed that the intracanalicular part of the optic nerve was entirely supplied by the ophthalmic artery (8-12). Several small branches (usually one to three in number) arose from the ophthalmic artery near the apex of the orbit. These branches reached the optic nerve by transversing the connective tissue bands that bind the optic nerve to the surrounding dural sheath (11,12). No axial vascular system was seen in Hayreh’s study. Our present study is in concurrence with Hayreh’s findings.

In the present study, we always found the origin of the ophthalmic artery to be from the internal carotid artery. As an unusual variant, it has been described to arise from the middle meningeal artery (8). The intracanicular course of the ophthalmic artery varied from the inferior medial position in the optic canal at the cranial end to the inferior lateral position at the orbital end (Table 1). Throughout its course, we found the intracanalicular ophthalmic artery to be almost entirely embedded in the dura. It then pierced the dural sheath of the optic nerve at the orbital end and became epidural in location. Under gross dissection, the intracanalicular ophthalmic artery seemed exposed under the dura. However, by careful microscopic examination, a thin layer of dura was always seen to wrap about the ophthalmic artery. Our finding differed from Hayreh’s report that the ophthalmic artery arises in the subdural space and pierces the dura on its inferior aspect (8).

The delicacy of the intracanalicular vasculature could be visualized well under the microscope. The optic nerve can be damaged by either concussive or compressive mechanisms, and in some cases both conditions can occur in the same patient (13-16). Interruption of the vascular supply to the intracanalicular optic nerve, either from a closed head injury that causes shearing of the pial network or from direct compression by a bony frag-
ment or hematoma, is the most widely accepted explanation of visual loss in traumatic optic neuropathy (7,11,16). Walsh, in his clinical-pathological correlations, found hemorrhages in the nerve, dura, and sheath space; tears in the nerve or chiasm; and contusion necrosis of the optic nerve to be the primary lesions in indirect trauma to the optic nerve (17). Similar reports can also be found elsewhere in the literature (18,19). These reports indicate the vulnerability of the intracanalicular capillary network to traumatic disruption and agree with our findings.

Habal and Maniscalco performed quantitative measurements of the optic canal (20,21). The postnatal growth of the optic canal and its relation to paranasal sinuses were described by Lang (22). Great variations existed in the measurement of this structure. This may partly reflect the inappropriate attempt to express the thickness or length of the optic canal by only one value, since the length and thickness of the optic canal varies not only from anterior to posterior, but also from medial to lateral. In the present study, the optic canal was totally removed en bloc from cadavers and then dissected under a stereomicroscope. Each of three levels of the canal was considered separately for measurement. Extremely thin walls, such as the medial wall and falciform ligament, were measured by means of a computerized semiautomated image analysis system and accompanying high-power microscopy. The middle medial wall was the thinnest part of the optic canal. In cases of traumatic optic neuropathy, this part might be most vulnerable to traumatic fracture. Twelve of 58 cases (21%) had a fracture of the medial wall of the optic canal, as seen by computed tomographic scan (23). In another report, however, five of 379 patients who suffered blindness from optic canal fracture were found to have lesser wing fracture by computed tomogram (24). The length of the falciform liga­ment varied from 1.80 mm to 6.30 mm, with an average of 3.83 mm, which was very close to the measurement of Renn and Rhoton (25). The sharp margin of this ligament can severely pinch the opti­cnergiewhen optic nerve edema occurs after head injury (20,21).

The equivalent diameters of the subdural space (Ds), calculated from the subdural transverse areas, were 1.46 mm, 1.39 mm, and 1.72 mm from anterior to posterior, respectively \( Ds = 2 \times (subdural transverse area)^{2} \). The middle part of the optic canal was the narrowest passage for the optic nerve and hence a likely site of injury in cases of edema or subarachnoid hemorrhage. This suggests an important consideration in the surgical management of traumatic optic neuropathy patients. For complete and adequate decompression of the optic canal, removal of much of the medial, and sometimes inferior, wall is necessary. Maniscalco and Habal emphasized the importance of removing the optic ring in the distal (orbital) portion of the optic canal (21). However, since the narrowest portion of the canal is in the middle portion, we emphasize the importance of opening this area in optic canal decompression.

REFERENCES

Annual Review

Ocular Motor Systems
Part 2: Nuclear and Supranuclear Systems

Barry Skarf, Ph.D., M.D.

This review covers selected articles dealing with the physiology of eye movements and their disorders. The articles appeared in the world medical and scientific literature during 1993. The subject matter and the review are divided into two parts. Part 1, which appeared in a previous issue of this journal, reviewed those articles concerned with infranuclear systems. Part 2, presented here, reviews those articles that deal with brainstem and cerebral processes mediating supranuclear and nuclear control of eye movements.

BRAINSTEM

Nuclear Palsies

Physiological and anatomical evidence has demonstrated that the abducens nucleus contains interneurons that project to the contralateral medial rectus subnucleus and that localized lesions of the abducens nucleus result in an ipsilateral gaze palsy. Hirose and co-workers presented a clinical/neuro-radiological correlation of this phenomenon (1). Their patient developed an acute left gaze palsy and a partial left internuclear ophthalmoplegia (INO; actually, an incomplete one-and-a-half syndrome, although they did not point this out) along with left lower motor neuron facial weakness. Magnetic resonance imaging (MRI) demonstrated a discrete lesion in the left pons involving the abducens nucleus, medial longitudinal fasciculus (MLF), and genu of the seventh nerve, sparing the paramedian pontine reticular formation (PPRF).

Acute, isolated cranial nerve palsies in vasculopathic patients are usually considered to be due to microvascular infarction along the affected nerve. A collection of seven cases of isolated or predominant ocular motor palsies due to brainstem stroke features five patients with oculomotor palsies, one superior oblique, and one abducens palsy (2). In each case, the clinical findings are well correlated with the neuroradiological findings. Function tended to improve within a few months. In most cases, there were other signs of a brainstem lesion, such as decreased supraduction of the contralateral eye (in three of the five oculomotor palsies) or trigeminal sensory loss. Such findings should raise the suspicion of brainstem stroke and lead to appropriate diagnostic investigations, including brainstem MRI. Truly isolated brainstem ocular motor palsies that cannot be distinguished from peripheral nerve lesions are rare.

Some controversy exists concerning the extent to which eye movements are affected in amyotrophic lateral sclerosis (ALS). In a recent article, Gizzi et al. (3) reported that ocular motor function is spared in ALS and that ALS patients who have significant eye-motion abnormalities must have additional pathology, such as Parkinson's disease, affecting other systems. These findings were disputed in the correspondence that followed (4,5). Taking a different approach to understanding ophthalmoplegia in ALS, Okamoto et al. (6) examined third and fourth nerve motor nuclei in 27 patients with ALS using histological and immunohistological techniques. In all cases, oculomotor neurons were relatively well preserved. In 11 of the 27 ALS patients, there were some rare but definite morphological changes similar to those in the anterior...
horns. The abnormalities were more frequent in those patients who also had dementia and were seen in all three patients who had ophthalmoplegia. The authors concluded that by the terminal stage of ALS, the third and fourth motor nuclei can be slightly affected in a manner similar to that of the anterior horns, but that in most cases, the degree is less than required for the development of ophthalmoplegia. They concluded that the majority of abnormal eye movements seen in ALS are supranuclear in origin.

A number of single-case reports described syndromes involving nuclear and infranuclear brainstem loci. A patient seen with “divergence paralysis” who was found initially to have a concomitant esotropia at distance, progressed to show clear evidence of bilateral abducens and unilateral facial palsies (7). The patient also developed unilateral gaze-evoked nystagmus. All studies were negative except for increased cerebrospinal fluid (CSF) protein, which returned to normal when the clinical findings resolved, prompting the authors to make a presumed diagnosis of incomplete Miller-Fisher syndrome.

Another unusual case of Miller-Fisher syndrome, requiring endotracheal intubation for 1 month, was described in a 2-year-old boy who initially was seen with left esotropia (8). The child progressed to develop complete external and internal ophthalmoplegia associated with limb ataxia and hyporeflexia and then developed a flaccid, areflexic quadriparesis over 3 days. The patient appeared to respond to treatment with plasmapheresis and immunoglobulin therapy, but full recovery took place over several months. All findings were attributed to a severe polyradiculopathy. No evidence of a central process was found, but MRI was not performed. An article in Polish reviewed the pathological mechanism and clinical aspects of Fisher syndrome, and concluded that both peripheral and central structures are probably involved (9).

One-and-a-half syndrome was described in a 45-year-old man with allergic granulomatosis and angiitis (AGA) who was in remission on maintenance prednisolone (10). Ocular findings improved on cyclophosphamide and increased prednisolone. Microangiopathy due to the AGA was thought to be the cause of the one-and-a-half syndrome, and its development suggests that long-term treatment with prednisolone and cyclophosphamide along with close monitoring of symptoms and peripheral blood eosinophilia might be indicated in severe AGA.

Another patient was described who developed one-and-a-half syndrome after surgery to resect a cavernous angioma from the floor of his fourth ventricle (11). This case was reported because the patient also described hallucinations after surgery, but these disappeared while the one-and-a-half syndrome persisted.

 Möbius syndrome consists of facial diplegia and bilateral horizontal gaze palsies, with convergence used for cross-fixation by some patients. It can be associated with a diverse spectrum of developmental anomalies, such as deafness and supranumerary digits, and with a wide variety of inheritance patterns. An infant was described with Möbius syndrome and Poland syndrome, cleft palate, dextrocardia, mandibular hypoplasia, and multiple areas of diffuse brain-volume loss associated with a t(1;11)(p22;p13) translocation (12). Because the translocation was present in his phenotypically normal father and brother, it may be coincidental or it may indicate the possibility of genetic heterogeneity for the Möbius disorder.

A constellation of congenital ocular motor defects is described in a patient with bifacial diplegia, right-sided ptosis, complete lack of vertical and rotary movements, large exotropia with defective adduction, bilateral optic disc colobomas, and a retinal detachment in the right eye (13). She developed simultaneous bilateral abduction with Bell’s phenomenon (i.e., both eyes abducted on forced eye closure). MRI scan demonstrated the fifth, seventh, and eighth nerves but failed to reveal the third nerve. The authors concluded that this patient has congenital defects involving bilateral second, third, fourth, and seventh nerves. Although the patient had evidence of bilateral abducens function, the authors maintained that their patient falls within the spectrum of Möbius syndrome. Whereas it is clear to this reviewer that the patient has a syndrome involving congenital cranial nerve palsies, her findings suggest a variant of bilateral synergistic divergence, a congenital condition in which there is defective adduction associated with bilateral abduction on attempted gaze to either side, or, alternatively, a variant of Duane’s syndrome.

Internuclear Ophthalmoplegia (INO)

An electrooculogram (EOG) study of 18 patients (14) with INO demonstrated that the occurrence, in the abducting eye, of overshoot dysmetria and dissociated nystagmus was often concomitant and related to the degree of interocular dissociation in saccadic velocities as measured by the Versional Disconjugacy Index (VDI) = (peak velocity of ad-
INO was described in an 18-year-old man who was
been described (14a). A case of traumatic bilateral
adaptive mechanisms that occur in this disorder.
abnormalities seen in INO are an expression of
Thus overshoot amplitude was found to be quan­
ducting eye)/(peak velocity of adducting eye).
and paraesthesia around the corner of the mouth
man with migraine, who developed sudden onset
both brainstem levels were found in a 22-year-old
articles dealt with lesions in the pons. Lesions at
sions appeared this year, whereas relatively few
Premotor (Supranuclear) Brainstem Lesions
 Several articles describing thalamic–midbrain le­
sions appeared this year, whereas relatively few
articles dealt with lesions in the pons. Lesions at
both brainstem levels were found in a 22-year-old
man with migraine, who developed sudden onset
of a pupill-sparing third nerve palsy, hemiparesis,
and paraesthesia around the corner of the mouth
and in the thumb and index finger on his left side
(19). MRI showed infarcts in the midbrain tegmen­
tum bilaterally and in the right pons, which were
attributed to basilar artery migraine. There were
no lesions in the cerebral or cerebellar hemi­
spheres. The ophthalmoplegia resolved within 12
h, and all symptoms disappeared within 10 days.
Basilar artery migraine is a most unusual cause for
an infarction in this region.

Two cases of selective downgaze palsy with dis­
crete bilateral lesions in the region of the rostral
intersitial nucleus of the MLF (riMLF) demon­
strated by MRI were described by Green et al. (20).
One patient was a 9-year-old girl who developed a
bilateral midbrain–thalamic infarction after severe
pneumococcal meningitis, whereas the second, a
64-year-old man, suffered a midbrain stroke with
well-demarcated bilateral lesions just rostral to the
red nuclei and anterolateral to the cerebral aque­
duct. In both cases, the infarctions were in the ter­
ritory of the posterior thalamic paramedian artery,
a branch of the basilar communicating artery. This
article supported the considerable body of experi­
mental and pathological data that assign control of
downgaze to both rostral intersitial nuclei of the
MLF and that require bilateral lesions of the riMLF
to produce selective downgaze palsy. The au­
thors pointed out that both patients also had mild
slowing of upgaze saccades and concluded that ar­
eas critical for upgaze lie just dorsal to the riMLF
and are rarely spared completely with bilateral
midbrain lesions (20).

Thalamic–midbrain lesions can cause other ocu­
lar motor mischief: Galetta et al. (21) described a
48-year-old man who developed a right third nerve
palsy and contralateral paralysis of supraduction
with eyelid retraction. MRI demonstrated an in­
farct in the region of the nucleus of the posterior
commissure (NPC) and third nerve fasciculus. The
patient also had left fifth, sixth, seventh, and
eighth cranial nerve palsies due to a lesion in the
left pons. He also had dysarthria, decreased gag,
tongue protrusion to the left, left flaccid hemipa­
resis, hemisensory loss, hyperreflexia, and plantar
extensor response. Unilateral lesions of the NPC
have been implicated in the development of bilat­
eral lid retraction (22). The ipsilateral third nerve
palsy masked the lid retraction that presumably
would be present in the right eye, resulting in this
"plus-minus" lid syndrome (23). The left supra­
duction deficit is presumably due to involvement
of the right third nerve nucleus or to a lesion in the
midbrain producing an upgaze palsy.

Although midbrain lesions clearly can cause ver­
tical gaze palsies, similar vertical gaze deficits have
been erroneously attributed to exclusively thalamic lesions. Siatkowski et al. (24) argued convincingly that, in these cases, thalamic lesions (usually infarctions) must coexist with midbrain pathology, and it is the midbrain lesion that is directly responsible for the ocular motor disturbance. This conclusion is based on the fact that both thalamus and mesencephalon share a common blood supply and that reports describing the localization of responsible lesions to the thalamus have always been based on CT scans, which cannot adequately distinguish lesions of the upper midbrain from thalamic lesions. The true extent of these lesions can be demonstrated only with MRI of the mesencephalon, which is recommended in all patients with vertical gaze dysfunction.

As if to emphasize this point, four cases of "dorsal midbrain syndrome" due to unilateral vascular lesions of the posterior medial thalamus and midbrain were presented in another study (25). However, the pretectal area and posterior commissure were involved in all cases. Supporting the diagnosis, each patient had vertical gaze paresis, convergence--retraction nystagmus (documented by EOG), lid retraction, and pupillary abnormalities. However, in two of the cases, the gaze deficit was for downward movements only, and convergence--retraction nystagmus was evoked only with attempted downgaze or convergence. The authors did not explain how patients with lesions of the posterior commissure were spared upgaze palsy. All four patients improved with time.

Rarely, upward-gaze palsy can be a sign of transtentorial upward herniation due to a large cerebellar infarction. A 63-year-old man with massive left cerebellar infarction was seen with vertigo, headache, and upgaze palsy; he also had right ptosis, left facial weakness, left-sided hearing loss, and ataxia of the left upper and lower extremities (26). He proceeded to lose consciousness over a few hours but improved after decompression of the posterior fossa. The authors pointed out that upward-gaze palsy can be an initial sign of massive cerebellar infarction that, in this setting, must be considered an indication for urgent surgical decompression.

Saad and Sanders described a most unusual patient with loss of infraduction in one eye and of supraduction in the other (27). They found an arteriovenous malformation in the rostral midbrain and claimed that this rare ocular motor abnormality should be attributed to interruption of supranuclear pathways for vertical gaze and not to a subnuclear lesion of the oculomotor nerve nuclear complex.

In a brief review article, Imai et al. (28) described the clinical spectrum and differentiating features of Dopa-unresponsive pure akinesia or freezing. This condition bears some similarity to parkinsonism but is different in that marked akinesia or freezing occurs without rigidity or tremor, and it is completely unresponsive to treatment with L-Dopa. The freezing symptoms affect gait, writing, and speech, and there is no dementia. One third of patients have apraxia of eyelid opening, and other ocular motor signs were usually present, including vertical-gaze palsy, convergence palsy, horizontal-gaze nystagmus, square-wave jerks, saccadic pursuit, and ocular flutter. Vertical optokinetic nystagmus (OKN), especially downward, was markedly decreased in all cases. Several patients were either diagnosed as or suspected of having progressive supranuclear palsy (PSP). Autopsy reports are available on only three patients, all diagnosed clinically as having PSP. Two had pallidodnigroluysian atrophy (PNLA), whereas the third had PSP. The authors noted the clinical similarity of these two conditions. They concluded that Dopa-unresponsive pure akinesia is closely related to the "PSP group" of syndromes including PSP, atypical PSP, forme fruste of PSP, and PNLA, but clearly more information is required to define these relationships and the underlying pathology.

Two articles (29,30) appeared this year dealing with benign paroxysmal tonic upgaze of childhood with ataxia. This benign, self-limited condition is characterized by bouts of tonic upward deviation of the eyes associated with ataxia in infants and young children (31). There is no actual ophthalmoplegia, and the patients make downward saccadic movements to compensate for the conjugated upward deviation of their eyes. During the episodes of tonic upward deviation, which occur daily, the patients are unsteady with ataxia and frequent falls. All laboratory, neuroradiological, and neuropathological (one case) studies have been normal. Three patients were described (29) who had definite family histories of this condition, suggesting that there is an autosomal dominant mode of inheritance, at least in some families. This was not mentioned in any of the previously reported cases. These three patients also had motor clumsiness between episodes and delayed acquisition of independent gait. Two of the cases showed improvement when treated with levodopa and carbidopa, and the authors recommended a therapeutic trial in all patients with this condition. Another single case of this condition was reported in a 9-month-old boy who also had cystic fibrosis (30). Moving down the brainstem, two new cases of
These authors emphasized that diplopia may be bilateral superior oblique overaction, the authors easily localized, such as multiple sclerosis (MS), native lesion to the midbrain pretectum predominantly studied patients with diseases that are not easily localized, such as multiple sclerosis (MS), trauma, or drug toxicity. They do not, however, mention how many patients with midbrain tumors were studied in 111 patients with either acute vascular brainstem lesions or MS. Measures were compared with those observed in 110 normal controls (37). Of 86 patients, 83% exhibited pathological ocular torsion of one (47%) or both (36%) eyes. Of 111 patients, 94% showed a pathological tilt of the subjective visual vertical. Most patients recovered gradually over 1 month. All unilateral brainstem lesions caudal to the upper pons were found to cause ipsiversive ocular torsion of one or both eyes, with concurrent ipsiversive tilts of the subjective visual vertical. All lesions rostral to this pontine level produced contraversive tilts in both measures. This finding supports the concept that ascending projections from the vestibular nuclei to the interstitial nucleus of Cajal decussate in the pons or caudal midbrain (35).

For those who can read German, an extensive and well-illustrated review of basic physiology and disorders of the vestibulo-ocular reflex, optokinetic nystagmus, and smooth pursuit eye movements is available (38).

The ocular tilt reaction (OTR) is the clinical triad of head tilt, conjugate ocular torsion, and skew deviation produced by damage to the utricle and its brainstem projections. Although animal and human studies indicate that the labyrinth, lateral vestibular nucleus, and interstitial nucleus of Cajal all contribute to the OTR, most reported cases have involved brainstem lesions [for an exception, see Halmagyi et al. (34)]. It is of interest, therefore, that two recent articles described the development of OTR after vestibular neurectomy or labyrinthectomy or both to treat acoustic neuroma or Meniere’s disease (35,36). Four patients, reported by Wolfe and co-workers (35), experienced vertical diplopia after this surgery, and their double vision prompted neuro-ophthalmological consultation. These authors emphasized that diplopia may be the only symptom in patients with OTR. In all four cases, diplopia resolved within 3 months. In contrast, Vibert et al. (36), who described a single patient, argued that OTR caused by peripheral nerve lesions is probably underrecognized because the diplopia and other subjective components are masked by oscillopsia and nystagmus resulting from vestibular neurectomy. The evanescent nature of the vertical and cyclotorsional deviations produced by peripheral lesions make their presence hard to recognize. In the case described, diplopia and skew deviation resolved within a few days, but conjugate eye cyclotorsion lasted weeks (36).

In the same theme, monocular and binocular ocular torsion and tilt in subjective visual vertical were studied in 111 patients with either acute vascular brainstem lesions or MS. Measures were compared with those observed in 110 normal controls (37). Of 86 patients, 83% exhibited pathological ocular torsion of one (47%) or both (36%) eyes. Of 111 patients, 94% showed a pathological tilt of the subjective visual vertical. Most patients recovered gradually over 1 month. All unilateral brainstem lesions caudal to the upper pons were found to cause ipsiversive ocular torsion of one or both eyes, with concurrent ipsiversive tilts of the subjective visual vertical. All lesions rostral to this pontine level produced contraversive tilts in both measures. This finding supports the concept that ascending projections from the vestibular nuclei to the interstitial nucleus of Cajal decussate in the pons or caudal midbrain (35).

For those who can read German, an extensive and well-illustrated review of basic physiology and disorders of the vestibulo-ocular reflex, optokinetic nystagmus, and smooth pursuit eye movements is available (38).

**Cerebellar Lesions**

Cerebellar infarction is relatively uncommon, representing ~1.5% of strokes. A clinical and radiological review of 66 patients with cerebellar infarcts revealed that lesions in the posterior inferior cerebellar artery (PICA), and superior cerebellar artery (SCA) distributions have distinct differences in clinical presentation, course, and prognosis (39). Infarcts in the PICA distribution are seen with vertigo, headache, and gait imbalance and had a tendency to be life threatening because of brainstem compression from postinfarct swelling. Patients with SCA infarcts had gait and limb ataxia at onset with much less vertigo and headache and generally had a benign clinical course. Of interest to neuro-ophthalmologists, 75% of patients with PICA infarcts had nystagmus, whereas only 50% of patients with SCA infarcts had nystagmus. In both groups, the nystagmus was predominantly horizontal and beat either ipsilaterally or bilaterally.
Fewer than 6% of the patients in each group manifested horizontal contralateral nystagmus exclusively. Of PICA infarcts, 11%, and 7% of SCA infarcts were associated with vertical nystagmus. The authors pointed out that no elements in the bedside analysis of the nystagmus allowed a distinction to be made between the two vascular territories. In particular, they noted that vertical upbeating nystagmus, thought to be associated with vermian lesions, was not a feature of SCA cases, although these cases frequently involved the superior vermis. In concluding, this article emphasized the importance of monitoring brainstem signs during the early stages of cerebellar swelling. The onset of ipsilateral sixth nerve palsies or horizontal gaze palsy is likely to indicate direct lateral pontine compression as a result of postinfarction cerebellar swelling, requiring emergency posterior fossa decompression.

In a single case, ocular flutter-like oscillations occurring on refixation were observed and recorded with EOG for the first time in a patient with a chronic history of human T-cell lymphoma virus type 1 (HTLV-I)-associated myelopathy.

A benign, presumably autosomal dominant, vestibulocerebellar disorder with prominent ocular motor abnormalities, seen in early childhood (but not congenitally), was described in 10 family members. Impairment or absence of smooth pursuit and vestibulo-ocular reflex (VOR) suppression associated with gaze-evoked and rebound nystagmus, slow build-up of OKN, mildly hyperactive VOR, and a high incidence of strabismus were noted in affected individuals. Most patients were asymptomatic, except for strabismus, and the condition was remarkable for the absence of other cerebellar signs.

CEREBRAL HEMISPHERES

Eye movements were recorded in 10 individuals who developed conjugate eye deviation (CED) after hemispheric stroke. These patients were part of a larger group of 74 cases of CED who were observed clinically. All 74 patients had at least some difficulty making saccadic and smooth pursuit movements in the contralateral direction. Recovery of clinically evident CED occurred in all patients who survived. The duration of the recovery period varied between 1 and 65 days. Some patients with prolonged recovery periods had preexisting lesions of the contralateral hemisphere, and generally the responsible lesions in these patients were larger than the lesions of the entire group. Eye movement were recorded serially for 6 months after recovery of CED. These studies demonstrated that contralateral saccades had prolonged latencies and hypometric amplitudes and that ipsilateral saccades also had slightly prolonged latencies, compared to controls. After recovery of CED, smooth pursuit movements were disturbed to both sides but were generally worse in the ipsilateral direction. Subtle abnormalities were still present at 6 months in most patients. Based on the observations that during CED, smooth pursuit movements are more limited in a contralateral direction but that after the disappearance of CED, there was asymmetry symmetry of smooth pursuit in the ipsilateral direction, the authors postulated that during CED, a spatial defect must predominate, prohibiting contralateral smooth pursuits. To support this, they noted that nearly all patients with CED show one or more manifestations of neglect. They concluded that the pattern of abnormal eye movements seen in their patients implies an important influence from the parietal lobe and from hemispatial neglect.

A selective contralateral saccadic palsy associated with contralateral supranuclear facio-palatopharyngeal paresis resulted from a small hematoma in the corona radiata adjacent to the genu of the internal capsule. On CT, the lesion was only 7 mm in diameter. This correlation suggests that the descending pathway from the frontal eye field in humans may pass through the genu along with the corticobulbar tract.

An infant born at 27 weeks of gestation was evaluated at 5 months of age with electro-oculography and VEPs when he was noted to be visually unresponsive. Smooth pursuit and OKN could be elicited only with movement of the target or surround to the left. In contrast, saccades were symmetrical in both directions. This finding, coupled with an asymmetrical occipital distribution of the flash and pattern VEPs, strongly suggested a right-sided posterior hemispheric lesion involving the occipital and parietal areas. A large hemispheric cyst was confirmed on imaging studies. The authors pointed out the usefulness of noninvasive techniques in neuro-ophthalmological investigations of preverbal children and infants.

To evaluate the lateralizing significance of head and eye deviation associated with seizures, 29 patients were studied with generalized tonic-clonic seizures that had a clearly defined lateralized focus. The traditional dictum that head- or eye-turning is produced by an irritating lesion in the contralateral hemisphere, was found in 90% of seizures, but only when the movement occurred within 10 s of generalization or continued as the...
seizure generalized. In contrast, the direction of the deviation was ipsilateral in more than 90% of seizures when the movement ended more than 10 s before the seizure began to generalize.

Oculogyric crisis and retrocollis are described in a 50-year-old man with bilateral putaminal hemorrhages (46), supporting the association between focal dystonia and bilateral lesions of the putamen.

NYSTAGMUS

Congenital Nystagmus

Persons with congenital nystagmus (CN) rarely experience oscillopsia. To investigate whether extraretinal signals (effference copy and proprioception) can contribute to the cancellation of retinal image motion produced during CN, Bedell and Currie tested four subjects by having them point in the perceived direction of targets that were flashed for 2 ms in total darkness (47). The pointing errors made by the subjects varied systematically according to the phase of the nystagmus waveform during which the target was presented, but were only 25% of the amplitude that would be expected if there were no extraretinal signals available. Therefore, the authors concluded that extraretinal signals can compensate for 75% of the changes in eye position that occur during the nystagmus cycle and that they may play a role in preventing oscillopsia.

Retinal image motion is increased in patients with nystagmus, and whereas it frequently degrades visual acuity, it also tends to degrade accommodative function (48). Patients with CN were found to exhibit marked variability in their accommodative function and abnormal depth of focus. There was no significant difference in accommodative function between albinotic or idiopathic groups of CN patients.

In another study, however, there was a difference between the VEPs recorded from the single albinos member of a family with idiopathic CN and other family members (49). Only the albino patient exhibited the contralateral VEP asymmetry, which is a marker for the visual fiber misrouting characteristic of albinos. Conversely, then, idiopathic CN cannot be attributed to the same structural or functional abnormality in reinnovate projections evidenced by the contralateral asymmetry in the VEP seen in albinos.

Horizontal jerk nystagmus recorded using EOG from a single patient with oculocutaneous albinism was noted to reverse in direction when the patient was exposed to any extraneous light stimulation (50). The authors speculated that this phenomenon is probably related to sensory pathway abnormality found in albinism.

Idiopathic congenital motor nystagmus may have a variety of different etiologies and, if inherited, may show X-linked, autosomal dominant or recessive inheritance. A family with autosomal dominant CN and no significant loss of visual function was described in which the nystagmus cosegregates with a balanced 7;15 translocation, suggesting a possible localization for autosomal dominant CN (51). Two affected members of the family who were examined demonstrated horizontal nystagmus with a small rotary component.

The presence of a null zone of nystagmus and a dampening of nystagmus with convergence are two features of CN that can be exploited surgically to give better visual acuity and to alleviate anomalous head posture. Preoperative and postoperative binocular visual acuities and eye-movement recordings were compared in 18 patients with CN with head turn who underwent eye muscle surgery consisting of the Anderson-Kestenbaum procedure (seven patients) or the artificial divergence procedure (six) or both (five) (52). In all three groups, the null zone shifted toward the primary position. EOGs demonstrated a broadening of the null zone in the artificial divergence and combined groups, with only a modest enlargement in the Anderson-Kestenbaum group. There was also increase in foveation time for three of the patients in the artificial divergence group and for two patients in the combined group. One of six patients in the artificial divergence group and four of five in the combined treatment group had improvement in binocular visual acuity of two or more Snellen lines, and this can be attributed to increased foveation times. The authors recommended the artificial divergence procedure for all patients with CN and head turn with good binocular function and suggested using a combined procedure if fusional convergence is not capable of fully alleviating the head turn. They reserved the Anderson-Kestenbaum procedure for patients with poor binocular fusion.

Kommerell and Zee described two patients with esotropia and typical latent nystagmus who were able to release and suppress their nystagmus at will, when neither eye was occluded (53). The nystagmus evoked always beat toward the amblyopic eye but could be as strong as that which developed when the amblyopic eye was occluded. The authors speculated that these patients exerted voluntary control on their nystagmus by varying the suppression of visual input from their ambly-
Acquired Nystagmus

Two patients with acquired pendular nystagmus and oscillopsia were shown to obtain relief of their symptoms with improved visual acuity after alcohol ingestion (55). One patient had MS with brainstem and cerebellar involvement. The second patient had developmental anomalies and congenital severe myopia; pendular nystagmus was noted to increase gradually as his retinal function deteriorated with progressive retinal disease (detachment, hemorrhage, and degeneration). No other drugs were found that could mimic the beneficial effect of alcohol. The authors speculated that acquired pendular nystagmus might arise from deafferentation of the inferior olive, either from lack of visual input or from structural interruption of afferent pathways or both.

Another study of 37 patients with pendular nystagmus and optic neuropathy due to MS supports the view that afferent visual input to brainstem centers may play an important role in the generation of acquired pendular nystagmus (56). In 18 patients with dissociated nystagmus, the side with larger oscillations was always the one with evidence of the more severe optic neuropathy, when optic neuropathy was also asymmetric. In contrast, asymmetries in INO or cerebellar signs did not correlate with the side of nystagmus asymmetry. Because of this finding, it was suggested that the dissociation in pendular nystagmus might be due to the asymmetries in the optic neuropathy rather than to asymmetries in cerebellar or brainstem disease. In this study, all 37 patients also had cerebellar eye signs and other ocular motor abnormalities, including INO (24) saccadic dysmetria (15), macro-saccadic oscillations (six) and ocular flutter (one), gaze-evoked nystagmus (26), rebound nystagmus (four), convergence-evoked upbeat lid nystagmus (two), and convergence-evoked upbeat ocular nystagmus (four). The MRI findings were also of interest: seven of eight patients who underwent MRI had cerebellar or brainstem lesions, and the most consistent finding was a lesion in the dorsal pontine tegmentum (56).

Vegetative state is a clinical condition resulting from serious organic brain damage, characterized by "unaware wakefulness," typically alternating with sleep stages that can be indistinguishable from those occurring in normals (57). Spontaneous CNS nystagmus in six vegetative-state patients was documented across the sleep-wake cycle (58). During stage 1 of sleep, nystagmus decreased to between 37.5 and 75% of the amplitude observed in the "awake" state. Nystagmus was abolished in stage 2 and in slow-wave sleep, but episodes of nystagmus were observed during rapid eye movement (REM) sleep in all patients. The clinical significance of these findings is unclear because, in this limited sample, there appears to be no relationship between nystagmus density during REM sleep and patient outcome.

A number of single-case reports described different types of nystagmus developing as a consequence of a variety of neurological lesions. Inverted Bruns' nystagmus (course nystagmus to the side opposite the lesion, fine nystagmus to the same side as the lesion) was noted in a 9-year-old girl after a shunting procedure to drain two large arachnoid cysts at the cerebellopontine angle (60). It is suggested that the Bruns' nystagmus in this case was caused by asymmetrical function within the vestibular nuclei or flocculus or both.

A 49-year-old woman who was seen with acute onset of vertigo and spontaneous horizonto-rotatory nystagmus to the left was diagnosed with MS (61). Abnormalities in the left-sided auditory brainstem responses were demonstrated 2 days before the patient progressed to develop total hearing loss and persisted for at least 10 months, although hearing returned to normal by 10 weeks.

Downbeating nystagmus should always suggest a diagnosis of Chiari malformation and requires MRI of the posterior fossa. Two single case reports of patients with Arnold-Chiari malformation documented other etiologies that contributed to the development of nystagmus and oscillopsia in these patients (62,63). The first case report described the development of horizontal-torsional nystagmus with oscillopsia in a previously asymptomatic woman with Arnold-Chiari malformation 2 weeks after lumbar puncture (62). The nystagmus almost disappeared by 3 months after decompressive surgery. The authors cautioned that lumbar puncture may accentuate craniospinal pressure dissociation and precipitate neurological signs in patients with
Arnold–Chiari malformation and also pointed out that horizontal or torsional nystagmus (or both) can be a feature of this condition. Another patient with Arnold–Chiari malformation developed lithium-induced downbeat nystagmus and oscillopsia 1 year after starting the drug (63). The nystagmus resolved spontaneously when lithium was discontinued, and surgical decompression was not required. Although lithium toxicity can cause downbeating nystagmus on its own, the authors speculated that toxicity may have had an additive effect when combined with the mechanical compression resulting from the Arnold–Chiari malformation, and they advised neuroimaging of all patients with downbeating nystagmus, even when the nystagmus seems to be temporally related to the introduction of lithium therapy.

A patient with intermittent, reproducible downbeat nystagmus that developed when he turned his head to his left side was described (64). The episodes were attributed to transient occlusion of a dominant vertebral artery by an osteophyte at C-6 and were relieved with surgical removal of this osteophyte.

Keane (65) described a group of 14 patients with cysticercosis (from among his series of 224 cases) who exhibited severe and unusual ocular motor disturbances, including upbeat nystagmus, PAN, bilateral fourth nerve palsies, and oculopalatal myoclonus. Although the presence of papilledema and pretectal signs (in 78 and 134 patients, respectively) is much more common in cysticercosis, this diagnosis should be considered in all patients from areas in which it is endemic who have evidence of posterior fossa disease.

GENERALIZED NEUROLOGIC AND SYSTEMIC DISEASES

A number of articles described different characteristics of ocular motor function in patients with a variety of neurological conditions, such as MS. An oculographic study of reflex horizontal saccades in 65 patients with MS and in 50 normal subjects demonstrated that the saccadic duration to small-angle saccades was more sensitive than saccadic velocity or latency in detecting clinical and subclinical ocular motor abnormalities (66).

Creutzfeldt–Jakob disease (CJD) typically is seen with subacute dementia; abnormalities of eye movements are not usually prominent, except in a small group of patients who have a "cerebellar form." Three patients were described who were seen, early in the course of their disease, with abnormal eye movements that included PAN and slow vertical saccades (67). Gradually, all saccades and quick phases of nystagmus were lost, but periodic alternating gaze deviation persisted. At autopsy, two of the three patients had pronounced involvement of the cerebellum, especially of the midline structures. The patients who lost saccades also had involvement of the saccade-generating regions in the pons and midbrain. The authors advised that CJD should be considered in patients with subacute progressive neurological disease, even when dementia is overshadowed by ataxia and oculomotor finding (particularly PAN).

Eye movements were evaluated in 53 insulin-dependent diabetics and compared to those of 42 nondiabetic controls (68). Saccades made by diabetics had longer reaction times and decreased accuracy when compared to normals. Maximum pursuit velocities were also reduced at all target velocities in diabetic patients.

An extensive historical and scientific review of eye-movement abnormalities in schizophrenics appeared in German (69). Disorders of smooth pursuit and saccadic systems were described, illustrated, and copiously referenced. A prospective study of 70 patients in their first episode of schizophrenia examined smooth pursuit eye movements, among other parameters, and found that 51% of patients had eye-tracking dysfunction (70). The rate in this sample of patients with first-episode disease is consistent with the prevalence in other samples of acutely ill, chronic, and remitted schizophrenics. Because these abnormalities appear early in the course of the disease, before treatment with neuroleptics in most cases, the authors concluded that the abnormalities are a consequence of the disease rather than the effects of chronicity, drug treatment, or institutionalization.

Opsoclonus–myoclonus (OM) syndrome is a paraneoplastic condition most frequently associated with neuroblastoma in children. Case reports that appeared this year provided the first description of a patient with Hodgkin's disease who developed severe opsoclonus and myoclonic movements of the head and limbs 7 weeks after she was treated with high dose BEAM chemotherapy (BCNU, etoposide, cytarabine, melphalan; 71). At that time, she still had a persistent mediastinal mass, which was treated with localized radiotherapy. She also received i.v. methylprednisolone, and her symptoms gradually resolved. The authors discounted the possible role of the cytotoxics in producing this clinical picture, because this effect has not been reported and because 8 weeks elapsed between the last course of treatment and the onset of neurological symptoms.
A 21-month-old child was described with OM of unknown etiology (72). Extensive investigation was negative, but this child initially responded to prednisolone but later relapsed. The authors pointed out that in this case, treatment with human immunoglobulin (Sandoglobulin) failed to benefit the patient. After 9 months, a course of prednisolone combined with low-dose azathioprine resulted in significant improvement. Steroids were tapered after 4 weeks, but the azathioprine was maintained with continued good effect.

Adrenocorticotropic hormone (ACTH) can also be used in the treatment of OM. Some OM patients, however, may develop antibodies to exogenous ACTH (73). This may explain the loss of efficacy of ACTH with chronic use in this syndrome. It is suggested that antibodies to ACTH should be sought in patients with OM who fail an ACTH trial, exhibit tolerance to ACTH, or who have undergone prolonged ACTH treatment. The article also pointed out that direct assays of ACTH may not measure ACTH that is bound to antibody and that an indirect assay of ACTH may be required to uncover true serum levels.

A patient with an occult malignant lymphoma of the brain had findings suggestive of OM (74). She had a lesion in the left dentate nucleus, which initially responded to oral prednisolone. When she relapsed, brain biopsy disclosed the true diagnosis, and she was treated with radiation therapy with partial response to oral prednisolone. When she required to uncover true serum levels, the article also pointed out that direct assays of ACTH should be sought in patients with OM who fail an ACTH trial, exhibit tolerance to ACTH, or who have undergone prolonged ACTH treatment. The article also pointed out that direct assays of ACTH may not measure ACTH that is bound to antibody and that an indirect assay of ACTH may be required to uncover true serum levels.

A patient with an occult malignant lymphoma of the brain had findings suggestive of OM (74). She had a lesion in the left dentate nucleus, which initially responded to oral prednisolone. When she relapsed, brain biopsy disclosed the true diagnosis, and she was treated with radiation therapy with subsequent disappearance of her opsoclonus, myoclonus, and ataxia.

REFERENCES
