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Long-term Visual Outcome in Patients With Anterior Visual Pathway Gliomas

Gregg S. Gayre, MD, Ingrid U. Scott, MD, MPH, William Feuer, MS, Timothy G. Saunders, MD, and R. Michael Siatkowski, MD

Objectives: To investigate the visual outcomes of patients with gliomas of the anterior visual pathway and the clinical features associated with prognosis.

Materials and Methods: During retrospective review, demographic and clinical data were abstracted from medical records of patients seen at the Bascom Palmer Eye Institute between January 1, 1970 and December 31, 1998.

Results: Of the 42 patients identified, 68% were female, and 55% had neurofibromatosis (NF) type I. There was no substantial difference in presenting signs, symptoms, and visual acuity between the NF(+) and NF(−) groups except for nystagmus, which was more common in the NF(−) group (p = 0.014). Throughout follow-up evaluation, vision in the better eye remained stable in both groups, independent of treatment or NF status. Vision in the worse eye often declined, despite treatment. However, binocular visual status, measured as average weighted logMAR (MAR, minimum angle of resolution) vision, did not change significantly over time, regardless of treatment or NF status.

Conclusions: In the NF(+) and NF(−) groups, vision in the better eye remained stable, regardless of treatment, and vision in the worse eye often declined, despite treatment. Binocular visual acuity (measured as weighted logMAR) did not change significantly over time, regardless of NF status or treatment modality.

Key Words: Glioma—Anterior visual pathway—Visual outcome.

Gliomas of the anterior visual pathway, with or without contiguous involvement of the hypothalamus, are rare tumors that occur most commonly in childhood. They constitute 0.8 to 5.1% of all childhood intracranial tumors and typically appear histologically as low-grade astrocytomas (1–5).

Optic gliomas occur commonly in neurofibromatosis (NF), a multisystem disorder that affects 1 in 3000 to 4000 people. The reported incidence of NF-1 in patients with optic pathway gliomas ranges from 10 to 70% (6–17). The incidence of optic gliomas in patients with NF-1 is as high as 15 to 21%, with symptomatic visual loss in approximately 20% of affected people (16,18–20). However, the incidence of progressive neurologic dysfunction appears lower in patients with NF and optic glioma, perhaps suggesting a less aggressive variant of glioma in patients with NF (16,21).

Considerable controversy exists regarding the natural history and, therefore, the appropriate management of optic gliomas. Some studies advocate surgical resection for symptomatic prechiasmatic tumors and chemotherapy or radiotherapy for symptomatic chiasmal lesions (16,22). Other reports have failed to confirm any benefit of therapy with respect to long-term survival or visual function (9,16,23–27). The purpose of this study is to investigate the visual and anatomic outcomes of patients with optic gliomas and to investigate clinical features associated with prognosis.

METHODS

The study protocol was approved by the University of Miami School of Medicine Institutional Review Board. Records of all patients with optic glioma evaluated at the Bascom Palmer Eye Institute between January 1, 1970 and December 31, 1998 were reviewed. Demographic and clinical data were abstracted from patients’ medical records.

Proportions were compared with the chi-square test with Yates correction; when expected values were small, exact (permutation) tests were used. Means were compared by the Student t test; however, when parametric assumptions were violated, the two-sample Wilcoxon test was used. Time to progression was analyzed with the Kaplan–Meier method and the log-rank test was used to assess statistical significance.
RESULTS

Forty-two patients with glioma of the anterior visual pathway were identified. Basic demographic information is summarized in Table 1. Twenty-three of 42 (55%) patients had NF-1. Seventeen percent of the patients presented before age 2 years, 31% between ages 2 and 5 years, 24% between ages 5 and 10 years, and 31% after the age of 10 years. Eighty percent of patients were Caucasian, 15% were Hispanic, and 5% were African-American. Mean duration of follow-up evaluation for all patients was 108 months (range, 3.6 to 23 months). Sixty percent of the patients had been monitored for 5 or more years.

In the NF(+) group, 13 of 23 (57%) patients had been diagnosed with NF before the detection of optic glioma. Among the 10 of 23 (43%) patients diagnosed with NF at or after detection of glioma, 70% were diagnosed within 1 month, 80% within 6 months, and 100% within 1 year after diagnosis of optic glioma (Fig. 1).

Common presenting symptoms in both groups were vision loss, headache, and proptosis (Table 2). Nystagmus was significantly more common in the NF(-) group (p = 0.014). Typical findings on initial examination for NF(+) and NF(-) patients included decreased acuity, optic atrophy, and visual field defect (Table 2).

The mean age at presentation was 13.7 years for patients with isolated optic nerve involvement and 9.6 years for patients with chiasm/hypothalamic involvement. This difference was not statistically significant (p = 0.34).

Two patients died during the follow-up period. Although both deaths occurred in the NF(-) group, this result was not statistically significant (p = 0.20). Neither death was related to glioma or associated complications.

As shown in Table 3, there was no significant difference in presenting visual acuity between the NF(+) and NF(-) groups. Among all patients, mean acuity was 20/37 in the better eye and less than 20/200 in the worse eye.

Visual field defects were seen on presentation in both groups. Seven of 19 (37%) NF(-) patients and 7 of 23 (30%) NF(+) patients had monocular field defects. Five of 19 (26%) NF(-) patients and 2 of 23 (9%) NF(+) patients had bilateral field defects. The frequency of bilateral deficits was three times higher in the NF(-) group than in the NF(+) group, but this difference was not statistically significant (p = 0.21). Seven of 19 (37%) NF(-) patients and 14 of 23 (61%) NF(+) patients had no evidence of visual field defect on initial examination.

Seven of 19 (37%) NF(-) patients and 9 of 23 (39%) NF(+) patients presented with isolated optic nerve involvement. The frequency of chiasmal involvement at presentation was similar in both the NF(+) or NF(-) groups (p = 0.99).

Two of seven (29%) NF(-) patients and five of nine (56%) NF(+) patients without initial chiasmal involvement progressed to chiasmal involvement during follow-up.

### TABLE 1. Patient demographics

<table>
<thead>
<tr>
<th>NF(-)</th>
<th>NF(+)</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>19</td>
<td>23</td>
</tr>
<tr>
<td>Number of patients</td>
<td>25 (60%)</td>
<td>25 (60%)</td>
</tr>
<tr>
<td>Mean age at presentation (years)</td>
<td>12.8 (4-54)</td>
<td>9.8 (5-69)</td>
</tr>
<tr>
<td>Family history of NF</td>
<td>0</td>
<td>9 (39%)</td>
</tr>
<tr>
<td>Family history of glioma</td>
<td>2 (9%)</td>
<td>2 (5%)</td>
</tr>
</tbody>
</table>

NF: neurofibromatosis.

### TABLE 2. Presenting signs and symptoms in the NF(+) and NF(-) groups

<table>
<thead>
<tr>
<th>Presenting signs</th>
<th>NF(-)</th>
<th>NF(+)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure</td>
<td>13 (33%)</td>
<td>22 (92%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>12 (30%)</td>
<td>13 (57%)</td>
<td>0.75</td>
</tr>
<tr>
<td>Vision deficit</td>
<td>10 (26%)</td>
<td>12 (53%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Endocrine dysfunction</td>
<td>10 (26%)</td>
<td>9 (39%)</td>
<td>0.54</td>
</tr>
<tr>
<td>Spasmus nutans</td>
<td>9 (23%)</td>
<td>6 (26%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Proptosis</td>
<td>7 (18%)</td>
<td>7 (30%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Optic atrophy</td>
<td>4 (10%)</td>
<td>5 (22%)</td>
<td>0.45</td>
</tr>
<tr>
<td>Decreased acuity</td>
<td>3 (8%)</td>
<td>5 (22%)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

* Difference between NF(+) and NF(-) groups, assessed with the Fisher Exact Test.
NF: neurofibromatosis.
patients demonstrated anatomic stability, whereas four patients (15%), need for tissue diagnosis (five patients, 42%), proptosis (six patients, 23%), hydrocephalus (four patients, 61%), accelerated tumor growth (11 patients, 43%) NF(+) patients were initially treated by observation. The majority (9/12, 75%) of the NF(+) patients who were observed throughout the follow-up period demonstrated anatomic stability without measurable tumor growth. Four of these stable cases were followed for more than 5 years. Two of these patients were NF(+), three had NF(-) groups, as well as observed versus treated patients. None of the three acuity measures demonstrated a difference in acuity change by NF status (best eye, p = 0.79; worst eye, p = 0.86; WMAR, p = 0.77; two-way analysis of variance); however, patients with a larger decrease in worse eye acuity and WMAR acuity were more likely to be treated (better eye, p = 0.25; worse eye, p = 0.005; WMAR, p = 0.012; two-way analysis of variance).

Eight of 19 (42%) NF(-) patients and 18 of 23 (78%) NF(+) patients were eventually treated during follow-up. As seen in Figure 1, five of seven (71%) patients who eventually developed chiasmal involvement did so within 12 months after diagnosis, although one NF(-) patient did so after 5 years. Sixteen of 19 (84%) NF(-) patients were eventually treated during follow-up, compared with only 10 of 23 (43%) NF(+) patients (p = 0.011). Treatment options included surgical resection, radiation, and chemotherapy. Indications for treatment included decreased vision (16 patients, 61%), accelerated tumor growth (11 patients, 42%), proptosis (six patients, 23%), hydrocephalus (four patients, 15%), need for tissue diagnosis (five patients, 19%), and/or endocrine dysfunction (four patients, 15%). There was no significant difference between the two groups in treatment modality chosen. All ten treated patients in the NF(+) group demonstrated tumor stability after initiation of treatment, as did 12 of 16 (75%) patients in the NF(-) group. In total, 22 of 26 (85%) treated patients demonstrated anatomic stability, whereas four (15%) patients demonstrated progression via serial neuroimaging (p < 0.5).

| TABLE 3. Presenting visual acuity (mean vision calculated on the logMAR scale and expressed as a Snellen fraction) |
|-----------------------------|-----------------------------|-----------------------------|
| NF(-) | NF(+) | Total |
| Better eye | Worse eye | Weighted logMAR |
| 20/46 | 20/418 | 20/60 |
| 20/31 | 20/184 | 20/49 |
| 20/37 | 20/267 | 20/61 |
| p value | p = 0.42 | p = 0.32 | p = 0.26 |
| (2 sample t test) |

NF, neurofibromatosis.

Table 4 displays logMAR (MAR, minimum angle of resolution) visual acuity in the better eye, logMAR visual acuity in the worse eye, and weighted logMAR (WMAR = 0.75 x better eye acuity + 0.25 x worse eye acuity) acuity changes during follow-up. Patients are divided into NF(+) and NF(-) groups, as well as observed versus treated patients. None of the three acuity measures demonstrated a difference in acuity change by NF status (best eye, p = 0.79; worst eye, p = 0.86; WMAR, p = 0.77; two-way analysis of variance); however, patients with a larger decrease in worse eye acuity and WMAR acuity were more likely to be treated (better eye, p = 0.25; worse eye, p = 0.005; WMAR, p = 0.012; two-way analysis of variance).

Figure 2A displays the visual fraction of the better eye of all patients plotted against the visual fraction of the worse eye. As demonstrated in this scatter graph, more than half of the patients maintained the acuity needed for a license to drive, as seen in the inner shaded area. Less than 25% of patients were legally blind based on acuity alone (points beyond outer shaded area). Figure 2B shows a similar plot for final acuity. Overall, there was little change in scatter graphs for presenting and final visual acuities.

Figures 3A through 3C display logMAR visual change by length of follow-up evaluation for better eye, worse eye, and WMAR. In the better eyes, only 4 of 42 (10%) patients experienced a significant drop in acuity of greater than 0.31 logMAR units (approximately 2 lines of Snellen acuity); all patients had been followed less than 5 years. Two of these patients were NF(+), three had initial visions better than 20/100, and all had been initially observed. In Figure 3B, logMAR acuity of the worse eye of all patients is plotted versus time. On average, logMAR acuity in these eyes decreased by 0.93, greater than 0.31 logMAR units (approximately 2 lines of Snellen acuity). However, this decline is significantly affected by 11 patients whose vision declined during an initial period of observation and declined further after treatment. In Figure 3C, weighted average logMAR change of all patients is plotted versus time. On average, weighted average logMAR acuity

| TABLE 4. logMAR change in vision |
|-------------------------------|-----------------------------|-----------------------------|
| Observed | Better eye | Worse eye | Weighted logMAR |
| NF(-), n = 3 | 0 ± (20/20 in all 3 eyes) | 0.17 ± 0.46 | 0.04 ± 0.12 |
| NF(+), n = 13 | -0.08 ± 0.21 | -0.01 ± 1.07 | 0.05 ± 0.28 |
| p = 0.4 | p = 0.4 | p = 0.4 |
| Treated | | | |
| NF(-), n = 16 | -0.10 ± 0.44 | -1.52 ± 1.80 | -0.45 ± 0.56 |
| NF(+), n = 10 | -0.26 ± 0.85 | -1.53 ± 1.24 | -0.59 ± 0.87 |
| p = 0.5 | p = 0.5 | p = 0.5 |
| Combined | | | |
| NF(-), n = 19 | -0.08 ± 0.41 | -1.25 ± 1.77 | -0.37 ± 0.54 |
| NF(+), n = 23 | -0.08 ± 0.60 | -0.67 ± 1.36 | -0.23 ± 0.68 |
| p = 0.5 | p = 0.5 | p = 0.5 |

LogMAR increases of -0.3, -0.7, -1.0, and -1.5 correspond roughly to a drop from 20/20 to 20/40, 20/100, 20/200, and 20/800, respectively.

NF, neurofibromatosis.
Eleven of 26 patients (42%) were eventually treated regardless of tumor location. Our data confirm that a process that prompted therapy or whether the treatment itself contributed to the further decline in vision after therapy was completed.

In Figure 4A, mean acuity of both eyes in the observed group is plotted versus time. No significant change in vision in either eye was observed. In Figure 4B, mean acuity of both eyes in the treated group is plotted versus time since initiation of treatment. When decline in vision before initiation of treatment is taken into account, visual stability after treatment is observed in both eyes.

**DISCUSSION**

Gliomas of the anterior visual pathway are rare tumors and may involve the optic pathway anywhere from the optic disc to the lateral geniculate body (28). First reported by von Graefe in 1864 (29), optic gliomas comprise 0.6 to 5.1% of all intracranial tumors, 1.7 to 7% of all gliomas, 1.5 to 3.5% of all orbital tumors, and 66% of all primary optic nerve tumors (7,15,16,23,30-36).

The clinical behavior of optic gliomas is related not only to their histopathologic characteristics but also to their anatomic extent. When isolated to the optic nerve, gliomas are relatively benign (37). However, when chiasmal involvement is present, prognosis is generally believed to be worse (4,37). The most important prognostic indicator has been reported to be extent of disease at presentation (5,38).

In a meta-analysis of 634 published cases of optic glioma, Dutton (16) found the mean age of presentation for all patients to be 8.8 years, similar to our finding of 10 years. Twenty-nine percent of patients in Dutton's study had a diagnosis of NF, compared to 57% in our series. According to Dutton (16), the majority (88%) of patients experiences some degree of visual dysfunction regardless of tumor location. Our data confirm that decreased visual acuity and visual field abnormalities are common. The prevalence of visual loss among our patients may actually be higher than reported; the young age of many of our subjects often made quantitative visual field data difficult to obtain, and some patients were evaluated before the era of modern automated perimetry. However, when weighted average logMAR vision is considered, the majority (74%) of patients maintained good visual function (better than 20/70 in at least one eye), regardless of initial anatomic extent or extent of tumor growth.
Throughout the years, great controversy has existed regarding the growth potential of optic gliomas. This dilemma has the greatest clinical consequences when confronting the patient with a glioma of the optic nerve and considering the possibility of posterior extension with chiasmal involvement and contralateral visual loss. Hudson (39) and others have argued that optic gliomas represent benign hamartomas with minimal potential for growth. Hoyt and Baghdassarian (40) believed that optic gliomas represent congenital nonneoplastic hamartomas with growth potential during early childhood only (16,39,40). Recently, however, Massry et al. (41) have established convincing evidence of the de novo occurrence of optic pathway gliomas in patients with previously normal neuroimaging. Our study reveals that although chiasmal involvement is common at presentation...
(perhaps supporting Hudson's theory), five patients in the NF(+) group and three patients in the NF(-) group demonstrated progression to chiasmal involvement after previously documented isolated optic nerve disease. Progression typically occurred within 1 year of presentation (71%). Some of these patients were evaluated before the era of modern imaging studies, and it is possible that some cases of progression may represent original misdiagnosis of unrecognized chiasmal disease because of limited sensitivity of older radiographic testing methods. Considering our data and that of Massry, clinicians should be aware that growth of these tumors is possible.

Dutton (16) found that among 114 cases of gliomas initially confined to the optic nerve and followed either conservatively or with partial resection, tumor progression was seen in 21%. For chiasmal gliomas followed conservatively, progression was observed in 29% during a follow-up period of 3 to 10 years. In a recent study by Erkal (5), 19 of 23 patients treated with radiation therapy at diagnosis of glioma demonstrated no evidence of anatomic tumor progression. In their study, visual improvement was observed in 50% of children with gliomas confined to a single optic nerve, whereas the remainder of the children demonstrated visual stability; vision improved in 34% of children with gliomas involving the chiasm and remained stable in 54% (5). Janss et al. (42), in 1995, demonstrated anatomic stability in three of ten patients treated with chemotherapy over a median of 3 years. In our study, anatomic stability was seen in 54% of NF(-) patients and in 100% of NF(+) patients receiving chemotherapy and/or radiation. In Dutton's study (16), vision remained stable in 91% of patients with gliomas isolated to the optic nerve, and was stable or improved in 76.8% of patients with chiasmal tumors managed with observation. In the current study, anatomic stability was noted in 14 of 17 (82%) observed patients.

The current study is unique in that it provides the most detailed long-term information in the literature regarding visual acuity of patients with optic glioma. In addition, in contrast to a meta-analysis, it carries the advantage of patients followed long term at a single center by a small group of clinicians. We find that visual function (as measured by average weighted logMAR acuity) was stable in NF(+) and NF(-) groups, and that legal blindness (based on acuity criteria) occurs in only a minority of these patients. Regarding treatment, vision did not change significantly in the better eye of either the observed or treated groups. However, a significant decline in vision in the worse eye of treated patients occurred before (prompting treatment) and after treatment in the group of patients in whom treatment was initiated after an initial period of observation. As stated before, we cannot determine what role, if any, treatment played in the continued decline of vision in this subgroup of patients.

In summary, in our study population, there was no significant difference in the presenting signs and symptoms of the NF(+) and NF(-) groups, with the exception of nystagmus, which was more common in the NF(-) group. There was no significant difference in presenting visual acuity, visual fields, or anatomic extent of tumor between the NF(+) and NF(-) groups. Chiasmal involvement occurred in both groups (26/42 patients). If chiasmal involvement was not present initially and did not occur (7/19 patients), it usually did so within the first 12 months after diagnosis. There was no difference in survival outcomes between the NF(+) and NF(-) patients.

Based on this retrospective nonrandomized study, we cannot make any specific therapeutic recommendations. However, when treatment was felt to be clinically indicated, it was associated with stability in tumor size in NF(+) and NF(-) groups. Throughout follow-up evaluation, vision in the better eye remained stable in the NF(+) and NF(-) groups, regardless of treatment. Vision in the worse eye often declined, despite treatment. However, binocular visual acuity (measured as weighted logMAR acuity) did not change significantly over time, regardless of NF status or treatment modality.

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Visual Activation in Functional Magnetic Resonance Imaging at Very High Field (4 Tesla)

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Objectives: Functional magnetic resonance imaging (fMRI) at very high field strengths provides functional brain mapping with the enhanced signal to noise ratio and the larger blood oxygenation level-dependent (BOLD) effect. We report activated areas in the standard space detected by fMRI at 4 Tesla (T) during simple visual stimulation.

Materials and Methods: Twelve healthy young subjects were scanned using a 4 T scanner during binocular flashing visual stimulation. Functional images were realigned to the first scan and then spatially normalized. Individual and group data analyses were performed to identify areas of visual activation.

Results: Activation of the bilateral primary visual cortex (V1/V2) was observed along the entire calcarine fissure in all subjects. The activated area extended to the extrastriate cortex in all subjects. Activation of the bilateral lateral geniculate nucleus (LGN) was detected in all subjects. The group data showed activation of the bilateral primary visual cortex and the bilateral lateral geniculate nucleus.

Conclusions: Robust activation of the vision-related areas was successfully obtained in all subjects using a 4 T magnetic resonance scanner. These results suggest that fMRI at very high field strengths may be effective in showing visual system physiology, and that it can be a promising method to assess visual function of human subjects.

Key Words: Functional magnetic resonance imaging—Visual activation—4 Tesla—Primary visual cortex—Lateral geniculate nucleus.

Functional magnetic resonance imaging (fMRI) of the brain with very high field strengths (> 3.0 Tesla [T]) has been performed during visual, motor, and cognitive tasks (1-11). The signal to noise ratio is greater at very high field strengths than at field strengths of most conventional scanners (e.g., 1.5 T scanners) (12), and the contribution of the capillaries to the signal change relative to that of large vessels can be increased by the use of magnetic resonance (MR) scanners with higher field strengths (13,14). Although signal changes in conventional MR scanners are relatively small (usually 1-3% for 1.5 T), previous studies at very high field strengths have shown greater signal changes of brain regions (1-3,12). Signal intensity changes can be more than 20% in the visual cortex (3). However, to our knowledge, activation pattern of fMRI at very high field during simple visual stimulation has not been described after image transformation to the standard brain, and variability in activation among subjects has not been well established.

The aim of this study was to describe the vision-related areas detected in 12 subjects by fMRI at 4 T. We used spatial normalization of the functional images to the standard space to report the location of activated areas and to perform group data analysis.

METHODS

Subjects and data acquisition
Twelve healthy volunteers (8 men and 4 women), ranging in age from 23 to 32 years, gave informed consent and participated in this study. Approval of the consent and protocol for this study was given by the Committee on Studies Involving Human Beings of the University of Pennsylvania. No subjects had a history of neurologic or ophthalmologic disease.

All studies were performed with a 4 T Signa scanner (General Electric Medical Systems, Milwaukee, WI) with a quadrature head coil. Three-dimensional axial images were acquired covering the whole brain for anatomic images (28 slices; slice thickness = 5 mm). Subsequently,
we selected a volume that covered the occipital lobe for functional image acquisition. Functional images were obtained using a gradient-echo echo-planar image (EPI) sequence (time to repeat [TR] = 2000 ms; echo time [TE] = 28 ms; matrix size = 40 x 64; field of view = 150 x 240 mm^2; 21 slices; slice thickness = 5 mm) after data for distortion correction were collected. The first 20 seconds of EPI data (ten scans) were discarded to remove the magnetic saturation effects.

Binocular full-field visual stimulation was provided by the light-emitting diode goggles (S10VSB; Grass Instruments, Quincy, MA). Subjects were wearing flashing goggles and were instructed to keep their eyes open. During the “rest” condition, the goggles were turned off for 20 seconds (ten scans). During the “task” condition, the goggles flashed at a rate of 8 Hz for 20 seconds (ten scans). The task condition alternated with the rest condition; the cycle was repeated six times, resulting in the acquisition of 120 scans during 4 minutes.

Data analysis
Data analysis was performed on UNIX workstations. IDL (Interactive Data Language, Boulder, CO) and SPM96 (Wellcome Department of Cognitive Neurology, London, UK) were used for data analysis. The first ten scans were discarded before transferring the data from the scanner to the workstations. Distortion correction files were used to correct geometric distortion in EPI images caused by residual magnetic field inhomogeneity, and this information was applied for the two EPI data sets of each subject. The anterior commissure (AC) was determined, and the origin for the EPI images was set on the superior edge of the AC. The EPI scans were realigned to the first scan. The realigned EPI images were spatially normalized to the standard space described by the Talairach and Tournoux atlas (“Talairach space”) (15) using the parameter derived from the 8-parameter affine transformation between the anatomic images and T1 template. The data were smoothed using an 8 x 8 x 10 mm full width at half maximum Gaussian kernel. A box-car delayed by 6 seconds was used as a reference function to account for the delay in hemodynamic response. The Z values for each subject were calculated for each voxel and converted to Z scores. Peak Z values within the visual cortex and lateral geniculate nucleus (LGN) of the thalamus were recorded. In addition, the mean Z value within the anatomically defined primary visual cortex was measured in each subject. The region of interest for the primary visual cortex was determined on the SPM T1 template.

The group SPMs were then constructed using the random effects kit (ftp://ftp.filion.ucl.ac.uk/spm/spm96_RFX.tar.gz). Each subject’s EPI scans were collapsed into one image per condition (i.e., two images for each subject). Finally, the SPM was created from twelve subjects’ images using the positron-emission tomography (PET) statistics routine. The activation maps were overlaid on the corresponding T1-weighted images of each subject or the T1 template of SPM96.

RESULTS
Single subject analysis
Robust activation was observed in the bilateral visual cortex in all subjects (Fig. 1 and Table 1). The area of activation with the highest Z scores extended along the entire calcarine fissure. The mean Z score within the anatomically defined primary visual cortex was 6.66. Although women (mean Z = 6.95, n = 4) had slightly higher Z values than men (mean Z = 6.54, n = 8), there was no statistically significant difference between sexes in the magnitude of primary visual cortex activation (standard normal test, p = 0.216, a two-sided test). In most subjects, distinct areas with high Z values comparable to the primary visual cortex were present more laterally and bilaterally (Fig. 1). The Talairach coordinates of these are consistent with those of MT/V5 (16).
All subjects showed activation in the bilateral LGN (17,18) (Fig. 1). Talairach coordinates of the maxima in the LGN activation are shown in Table 2.

**Group analysis**

The group analysis showed activation of occipital areas spanning along the calcarine fissure, and the maximal activation was found in this cluster (Fig. 2). The area extended to the parieto-occipital sulcus, where the most peripheral visual field is represented (19). The activated area possibly contained the area V2 as well as V1. The bilateral LGN activation was distinctly observed in the group data analysis (corrected $p < 0.05$), suggesting consistency in the location of the small area of LGN activation among subjects (Fig. 2).

**DISCUSSION**

In this study, we performed fMRI at very high field and postprocessed the functional images using spatial normalization, which transforms a single subject's images into a standard space. Spatial normalization enables us to perform a group data analysis, which is more appropriate in making inferences at the population level than an individual data analysis (20). The activated areas along the calcarine fissure were identified in individual and group data analyses, suggesting that this technique is capable of demonstrating activity of the primary visual cortex accurately. Also, the activated area included extrastriate cortex, although the extent of the area is variable among subjects. Such variability may result from the difference in subjects' attention levels (21). The activation of MT/V5 in most subjects can be explained by the fact that this area is well known to respond to flickering stimuli (22,23).

In addition to the visual cortex activation, bilateral activation of LGN was reliably obtained in all of the volunteers. The sensitivity of this measure was proven in the group data analysis as well as the individual data analysis. Chen and associates (8,9) used a similar visual stimulus and detected activation of the pulvinar nucleus of the thalamus as well as LGN activation. However, we did not find reliable activation of the pulvinar nucleus in this study. The discrepancy between their findings and ours may be explained by the difference in the statistical procedures, especially in the filter size in the spatial smoothing. Because the pulvinar nucleus is spatially close to LGN, it remains to be studied whether fMRI with higher spatial resolution reveals activation of the pulvinar nucleus using otherwise the same procedure as ours.

A robust response is the most important factor in clinical applications of fMRI and enhances the success rates of fMRI examinations (24). In this context, fMRI at very...
high field is a powerful tool for mapping cortical function. Further studies may include the use of more specific visual stimuli (e.g., motion, color, or form) to identify higher visual cortex.

REFERENCES
Epidemiology of Idiopathic Intracranial Hypertension in Israel

Anat Kesler, MD, and Natan Gadoth, MD

Objectives: To determine the incidence, demographic, and clinical features of Pseudo Tumor Cerebri (PTC)/Idiopathic Intracranial Hypertension (IIH) in Israel.

Materials and Methods: The chairpersons of all neurology and ophthalmology departments in Israel were asked to complete questionnaires regarding patients diagnosed with PTC/IIH from 1998 through 1999. Each questionnaire contained details regarding patient's age, sex, country of birth, age at diagnosis, weight, height, presence of obesity, and the results of lumbar puncture, brain computed tomography, magnetic resonance imaging, and/or magnetic resonance venography.

Results: Ninety-one patients with PTC/IIH were diagnosed during the years 1998 to 1999. Eighty-five (93.4%) patients were females and six (6.6%) patients were males. The calculated incidence of PTC/IIH in the Israeli general population was 0.57 to 0.94 per 100,000 persons, with incidences of 1.82 per 100,000 for women and 0.034 per 100,000 for men. The incidence for women during the childbirth years was 4.02 per 100,000. The female to male ratio was higher than previously reported for Western countries.

Conclusions: Although the population of Israel is a mixture of people originating from Eastern and Western countries, the incidence of PTC/IIH was found to be similar to that of Western countries. This finding is an additional support to the notion that PTC/IIH is more common in obese populations.

Key Words: Epidemiology—PTC—IIH—Obesity.

Pseudotumor cerebri (PTC) is the term commonly used for the association of increased intracranial pressure without clinical, laboratory, or radiologic evidence of an intracranial space-occupying lesion (1-3). However, idiopathic intracranial hypertension (IIH) may be a more suitable term (4). Thus, IIH will be used throughout this article.

To establish a diagnosis of IIH, the following criteria must be fulfilled (Table 1):

1) elevation of intracranial pressure (> 200 mm H2O),
2) normal cerebrospinal fluid (CSF) composition,
3) normal neuroimaging (except for empty sella),
4) normal neurologic examination, except for papilledema and abducens nerve paresis.

The typical patient with IIH is a young and obese female (1). Although IIH is usually a self-limiting condition, it may become chronic in some patients (5). The hospital incidence reported in several large series implies that IIH is a rare condition (2,5-9). In recent surveys, an annual incidence rate of 1 to 2 per 100,000 persons was found in the general population (1,6,7). The aim of this study was to determine the population-based incidence and provide the demographic and clinical features of IIH in Israel.

METHODS

The chairmen of all neurology and ophthalmology departments in Israel were personally asked to provide comprehensive details on patients with new onsets of PTC/IIH diagnosed in their institution during the years 1998 to 1999. They were required to complete a questionnaire containing the patient's age, sex, country of birth, age at diagnosis, weight, height, presence of obesity, lumbar puncture results, and the results of CT, MRI and/or MRV for each patient with PTC/IIH. A similar request was made through the Israel Medical Association Journal, which is distributed freely to all its members. Relevant demographic data were obtained from the Israeli Central Bureau of Statistics.

RESULTS

Of 22 hospitals providing tertiary medical care to the Israeli general population, seven small regional hospitals routinely refer patients with IIH to a major hospital. The
remaining 15 hospitals have an active neurologic department and ophthalmology or neuro-ophthalmology consultation services. We obtained complete data from 13 hospitals. Data were either unavailable or incomplete in two hospitals. Complete questionnaires for 91 patients with IIH who were diagnosed during 1998 to 1999 were received. There were no duplicate cases, as judged by names and identity card numbers.

Sinus vein thrombosis was excluded by contrast-enhanced computed tomography (CT) in all 91 patients. Additional neuroimaging was performed: magnetic resonance imaging (MRI) in 36 patients, magnetic resonance venography (MRV) in eight patients, and computed tomography venography (CTV) in three patients. Eighty-five (93.4%) patients were females and six patients (6.6%) were males. The females were younger than the males. Data regarding the presence of obesity were available in 63 patients (57 females and six males).

There were 36 obese patients, 35 were females. The presence of obesity was determined in 26 patients when body mass index (BMI) was greater than 30 kg/m². The presence of obesity could not be associated with age of onset or opening CSF pressure. The males were older, but this observation did not reach statistical significance (42.33 and 31.61 years, respectively; p = 0.174).

The Israeli population in the 1998 census was 5,970,000. Thus, the calculated incidence of IIH in the Israeli general population based on the current study was 0.94 per 100,000 persons, with the incidence for women 1.82 per 100,000 and men 0.98 per 100,000. The incidence for women during childbirth years (18–45 years) was 4.02 per 100,000. The population in the 1999 census was 6,100,000 persons, and the calculated incidence was 0.57 per 100,000.

The country of birth and ethnic origin was documented in 65 patients; 53 were born in Israel, five in the former Soviet Union, four in Morocco, two in Iraq, and one in the United States. The mean CSF opening pressure in females was higher than in males. Statistical significance, however, could not be calculated because of small sample size. The demographic and clinical data of the patients are shown in Tables 2 through 4.

### DISCUSSION

In this countrywide study, we obtained clinical and demographic information on patients with IIH diagnosed in the hospital setting in most neurology departments in Israel. Patients with IIH are customarily hospitalized in neurologic wards and seen concomitantly by a neurologist and an ophthalmologist or neuro-ophthalmologist. Moreover, lumbar punctures are performed only in neurologic wards. Thus, we believe that this group of patients represents IIH incidence in Israel during the years 1998 to 1999. The systematic and annual census performed yearly by the Israeli Bureau of Statistics enabled us to confidently calculate the yearly incidence rates of IIH for the period of this survey.

The incidence of IIH varies throughout the world. It is almost unknown in countries in which the incidence of obesity, a significant factor in the idiopathic form of this condition, is low, and is common in countries with an increased incidence of obesity. We found an annual incidence of 0.57 to 0.9 per 100,000 persons in the general population and 4.02 per 100,000 in females aged 15 to 45 years. A similar incidence was found by Durcan et al. (6) in Iowa and Louisiana (0.9 per 100,000 persons).

Radhakrishnan (1) reported an incidence of 1 per 100,000 persons in Rochester, Minnesota, whereas in Benghazi, Libya, it was 2.2 per 100,000 persons in the general population and 4.3 per 100,000 in women (10,11). Data on the incidence of IIH in several published studies are shown in Table 5. The incidence of IIH in countries such as Libya and Saudi Arabia is likely to be higher than in Western countries because of the higher prevalence of obesity among females of reproductive age (4,10). However, the geographic variation in the incidence of IIH requires additional epidemiologic studies.

The female preponderance and relatively high frequency of obesity found in many previous surveys (2,6,8,9) were also found in this study. The female to male

### TABLE 2. Clinical and demographic data on 91 patients with idiopathic intracranial hypertension

<table>
<thead>
<tr>
<th>Total</th>
<th>Females (n = 85)</th>
<th>Males (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, y</td>
<td>32.34 ± 11.01</td>
<td>31.62 ± 10.29</td>
</tr>
<tr>
<td>CSF opening pressure (mm H₂O)</td>
<td>340 ± 93.99</td>
<td>343 ± 95.35</td>
</tr>
</tbody>
</table>

CSP, cerebrospinal fluid.

### TABLE 3. Body dimensions in 63 patients with idiopathic intracranial hypertension

<table>
<thead>
<tr>
<th>Total</th>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obese (36)</td>
<td>35</td>
<td>1</td>
</tr>
<tr>
<td>57.2%</td>
<td>97.2%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Nonobese (27)</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td>42.8%</td>
<td>81.5%</td>
<td>18.5%</td>
</tr>
</tbody>
</table>

### TABLE 4. Distribution of patients according to ethnic origin and place of birth (n = 65)

<table>
<thead>
<tr>
<th>Place of birth</th>
<th>Israel (93.1%)</th>
<th>Other (6.9%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnic origin</td>
<td>Jewish (53.1%)</td>
<td>Arab (46.9%)</td>
</tr>
<tr>
<td></td>
<td>48 (73.65%)</td>
<td>17 (26.15%)</td>
</tr>
</tbody>
</table>

ratio was 14 to 1. This finding is higher than in Iowa (9)
and in Louisiana (3,6). This ratio was the lowest (1 to 8)
in the Johnson study (11). In a few studies, only females
were reported (10,12).

Obesity is a significant risk factor for IIH. In this
study, obesity was present in 97.2% of the females and in
only 2.8% of the males. Although these values concern
only 63 of the 91 patients whose body dimensions were
available or who were considered markedly overweight
according to personal subjective impression, they proba-
bley represent the whole study population.

In the report by Johnston and Paterson (11), only 34%
of patients were considered obese. Radhakrishnan (10),
using a definition of obesity as body weight greater than
20% of optimal, found that 74% of Libyan patients were
obese compared to 69% in Louisiana (6).

In Israel, a country with a large number of immigrants,
most patients with IIH were native Israelis. This might be
related to the fact that the peak of immigration to Israel
occurred between 1950 and 1960, and our patients are
mostly the offspring of those early immigrants.

The higher CSF opening pressure in females may be
secondary to obesity. Indeed, Mosek (13) recently
showed that opening CSF pressure is elevated in obese
subjects. On the other hand, Corbett and Mehta (14)
found that there was no significant statistical different
between mean CSF pressures in obese and nonobese
healthy subjects; however, those results were obtained
with a small sample size. The current study suffers from
several weaknesses:

1) It is a retrospective study.
2) Obesity was determined according to BMI in
27.7% of the obese patients only, whereas the other
72.73% were considered obese according to personal
impression.
3) Other causes of IIH such as hypervitaminosis A, ste-
roid withdrawal, and the use of certain drugs were not
included in the questionnaire. Because these condi-
tions are not common, the results were probably not
significantly affected.

In spite of its weaknesses, this study implies that IIH in
Israel is as common as in Western countries. This finding
probably reflects the increasing incidence of obesity in
Western communities.

Acknowledgments: The authors thank O. Abramsky, MD,
PhD; Y. Almog, MD; I. Bloch, MD; R. Carasso, MD; S. Dotan,
MD; Y. Goldhammer, MD; Y. Harishanu, MD; S. Honigmann,
MD; E. Kahana, MD; A.D. Korczyn, MD, MSc; J. Mannelius,
MD; M.J. Rubey, MD; E. Melamed, MD; B. Scharff, MD; M.
Sadeh, MD; Y. Vardi, MD; and D. Yarnitzky, MD for provid-
ing data on their patients.

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Do Men With Pseudotumor Cerebri Share the Same Characteristics as Women? A Retrospective Review of 141 Cases

A. Kesler, MD, Y. Goldhammer, MD, and N. Gadoth, MD

Objective: To determine whether males with pseudotumor cerebri (PTC) differ from females by clinical presentation, risk factors, and outcome.

Methods: The medical records of patients diagnosed with PTC or idiopathic intracranial hypertension (IIH) in two major university hospitals were obtained. Diagnostic criteria, clinical features, presence of obesity, mode of treatment, and outcome were tabulated.

Results: A total of 134 patients (18 males and 116 females) fulfilled the Dandy diagnostic criteria for PTC. Females and males shared similar clinical features and outcome. There was a substantial difference between the groups regarding body weight. The majority of females (77.8%) were considered significantly overweight, compared to 25% of the males.

Conclusion: Pseudotumor cerebri in males is relatively rare. The clinical features are identical to those found in females. The fact that the majority of the male patients had a normal body weight may indicate that increased body weight does not play a major role in causing PTC in men, whereas it is an established major risk factor in women.

Key Words: Pseudotumor cerebri—Intracranial hypertension—Obesity—Papilledema.

Pseudotumor cerebri (PTC), or idiopathic intracranial hypertension (IIH), is a disorder associated with intracranial pressure greater than 250 mm of water, normal neuroimaging (apart from possible small ventricles), and normal cerebrospinal fluid content (1).

The annual incidence of PTC in the general population is 0.9 per 100,000 people. Case control studies performed to date have shown a substantial association between PTC and obesity (2,3), which may be present in more than 90% of adult women with PTC. Although the established peak incidence of PTC in obese females aged 15 to 44 years is 7.9 per 100,000 people (4-6), there are no such data regarding males. Digre and Corbett (7) were able to provide only a relative percentage (16%) of males with PTC among their 187 patients; however, they quote rates ranging from 17 to 35% in a large series with more than 50 patients.

With PTC in males ranging from 6 to 50%, depending on the study (8-13), we were able to trace only one study in which the issue of PTC in males was addressed (7). According to this study by Digre and Corbett, 16% of the patients were males.

The present study was designed to review the symptoms, clinical course, and risk factors in males with PTC and to compare them with similarly affected females.

PATIENTS AND METHODS

We reviewed the medical records of 141 consecutive patients with PTC older than 14 years who fulfilled the Dandy criteria for PTC (10). All patients were diagnosed by two of the authors (AK and YG) during the period of time from 1982 to 1999, in the Neuro-Ophthalmology outpatient clinics of Meir General Hospital, Kfar Saba, or Sheba Medical Center, Tel-Hashomer, Israel.

Patients were regarded as significantly overweight ("obese") according to the examiner’s impression. Outcome was considered “resolved” when, after a year from onset, there was no evidence of optic atrophy, visual field defect, headache, or visual complaints. The designation “improved” was used for patients free of headache but with residual optic nerve damage. For statistical analysis, the Mann-Whitney U test was applied for age and diagnostic delay, whereas a chi-square value was calculated for the other parameters.

RESULTS

All 141 patients underwent contrast-enhanced cranial CT, and 47 patients also had a contrast-enhanced MRI. Only ten patients underwent additional magnetic resonance venography (MRV). None had a cerebral angiogram. Seven patients (three women and four men) were excluded because of sinus vein thrombosis (SVT). Thus, the study population consisted of 134 patients with PTC (116 females and 18 males). Fourteen males were diagnosed since 1990, and eight of those patients had an MRI (MRI was not available in Israel for routine use before...
Three males also had MRV. The mean age and age range for males and females were almost identical, with no significant difference regarding the age of diagnosis. There was a significant diagnostic delay in females compared to males. Data referring to body weight were recorded for 16 males and 107 females (88.8% and 92.2%, respectively). The majority of females (77.6%) were considered significantly overweight, compared to 25% of males.

In addition to papilledema, unilateral abducens nerve palsy was present in eight women and one man. The rest of the neurologic examination findings were normal in all 134 patients.

Headache was the most common complaint in both sexes. Transient visual obscurations (TVO) were more common in men (68.8% and 42.9%, respectively). Tinnitus was relatively rare.

Twenty-one females (18.1%) suffered permanent damage to both optic nerves. Seven (6.3%) had optic atrophy, and 18 (15.5%) had either a nasal field defect or constricted visual fields. Among the 15 males for which data regarding outcome were documented, ten were considered “resolved,” five suffered permanent optic nerve damage, two had optic atrophy, one had optic atrophy and nasal field defect, and two had a nasal field defect only.

Headache was the sole complaint reported by 50 females (43.10%) and 4 males (22.2%). Forty-four females and 11 males reported more than one symptom (37.93% and 61.1%, respectively). There was no difference in clinical features or outcome between overweight and normal-weight males.

The details of the various diagnostic, demographic, and clinical features for the entire patient population is shown in Table 1, and the characteristic data for each male patient is shown in Table 2.

Outcome was calculated separately for those patients whose symptoms and signs resolved or improved. Of the females, 57.5% were considered resolved, and 42.5% improved. Of the males, 68.8% resolved, and 31.3% improved. This difference was not significant \(p = 0.3\), Fisher exact test). A logistic regression model disclosed that all study parameters, including obesity, did not significantly influence outcome.

### TABLE 1. Clinical features of 134 patients with pseudotumor cerebri

<table>
<thead>
<tr>
<th>Feature</th>
<th>Females (116)</th>
<th>Males (18)</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y (range)</td>
<td>31.5</td>
<td>35</td>
<td>(p = 0.57)</td>
</tr>
<tr>
<td></td>
<td>(14-57)</td>
<td>(14-61)</td>
<td>(MW)</td>
</tr>
<tr>
<td>Diagnostic delay</td>
<td>28.4 weeks</td>
<td>14.57 weeks</td>
<td>(p = 0.25)</td>
</tr>
<tr>
<td>(3 days-1.5 years)</td>
<td>(a = 83)</td>
<td>(a = 14)</td>
<td>(MW)</td>
</tr>
<tr>
<td>Significant overweight, %</td>
<td>77.6</td>
<td>25</td>
<td>(p = 0.0002)</td>
</tr>
<tr>
<td></td>
<td>(83/107)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache, %</td>
<td>94.4</td>
<td>81.3</td>
<td>(p = 0.2)</td>
</tr>
<tr>
<td></td>
<td>(416)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TVO, %</td>
<td>42.9</td>
<td>68.8</td>
<td>(p = 0.053)</td>
</tr>
<tr>
<td>Abducens palsy, %</td>
<td>8.62</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Tinnitus, %</td>
<td>2.5</td>
<td>5.5</td>
<td>—</td>
</tr>
</tbody>
</table>

MW, Mann–Whitney U test; TVO, transient visual obscurations.

### DISCUSSION

This study summarizes our experience with a relatively large group of males with PTC. Previously, only one study, by Digre and Corbett (7), which was conducted prior to 1988, dealt specifically with PTC in males. Because obesity and endocrine abnormalities are not considered major risk factors for PTC in males today, occult causes, such as partial thrombosis of the cerebral sinuses, coagulopathies, and dural arteriovenous malformations (DAVM), should be considered. Indeed, most of our patients (14 of 18) were diagnosed after 1990 and thus had a CT with a much better resolution than previously available. Moreover, 8 of the 14 (57%) also had a contrast-enhanced MRI. With this finding in mind, we believe that SVT and significant DAVM were excluded. The more advanced neuroimaging may explain the lower rate of PTC in males (9.7%) in this study, compared to the 16% found by Digre and Corbett (7).

The diagnosis of PTC is readily suggested in a young obese female with papilledema. However, in a normal-weight male, headache and papilledema usually cause more concern about a mass lesion.

Headache is such a common complaint that unless ophthalmoscopy is not routinely and carefully performed, a significant diagnostic delay of PTC may result. It is not surprising that this delay was greater in our female patients, because women tend to complain about all types of headache (14) and are usually given the diagnosis of migraine.

In spite of the lack of data on precise body dimension measurements in our patients, it is still striking that only 25% of the males were considered significantly overweight, compared to 77.6% of females. In a recent unpublished study (Nitzan and Kaluski, Personal communication, Israel Health Nutrition Institute) conducted on 1100 healthy Israeli adults between March 1999 and January 2000, 37.1% of males and 28.1% of females were considered overweight (body mass index [BMI]: 25-30), whereas 16.7% of the females and 10.8% of males were considered obese (BMI > 30).

Hormonal changes are implicated as one of the causative factors for PTC (15). Accordingly, 17 of 116 females (14.6%) had evidence of hormonal dysfunction.
MEN AND WOMEN WITH PSEUDOTUMOR CEREBRI

TABLE 2. Clinical features of 18 males with pseudotumor cerebri

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age of onset (y)</th>
<th>Year of diagnosis</th>
<th>Significance of overweight</th>
<th>Associated conditions</th>
<th>Duration of symptoms before diagnosis</th>
<th>Symptoms</th>
<th>Recurrence</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/50</td>
<td>43</td>
<td>AN</td>
<td>Hypertension</td>
<td></td>
<td>1 year</td>
<td>Headache</td>
<td>Diamox</td>
<td>Resolved</td>
<td></td>
</tr>
<tr>
<td>2/70</td>
<td>65</td>
<td>BN</td>
<td>Hypercholesterolemia</td>
<td></td>
<td>2 months</td>
<td>Headache, TVO</td>
<td>Diamox, Prednisone</td>
<td>Improved, nasal field defect</td>
<td></td>
</tr>
<tr>
<td>5/21</td>
<td>16</td>
<td>AN</td>
<td>Hypertension</td>
<td></td>
<td>6 months</td>
<td>Headache, TVO</td>
<td>Diamox</td>
<td>Resolved</td>
<td></td>
</tr>
<tr>
<td>4/18</td>
<td>14</td>
<td>AN</td>
<td>Simitrizes</td>
<td></td>
<td>7 days</td>
<td>Headache, TVO</td>
<td>Diamox</td>
<td>Resolved</td>
<td></td>
</tr>
<tr>
<td>5/29</td>
<td>26</td>
<td>AN</td>
<td></td>
<td></td>
<td>3 months</td>
<td>Headache, TVO</td>
<td>Diamox</td>
<td>Resolved</td>
<td></td>
</tr>
<tr>
<td>6/53</td>
<td>46</td>
<td>BN</td>
<td>Hypertension</td>
<td></td>
<td>3 days</td>
<td>Headache, TVO</td>
<td>Diamox</td>
<td>Resolved</td>
<td></td>
</tr>
<tr>
<td>7/63</td>
<td>61</td>
<td>AN</td>
<td>Hypertension</td>
<td></td>
<td>7 days</td>
<td>TVO</td>
<td>Diamox</td>
<td>Resolved</td>
<td></td>
</tr>
<tr>
<td>8/36</td>
<td>30</td>
<td>AN</td>
<td></td>
<td></td>
<td>1 month</td>
<td>Headache</td>
<td>Diamox</td>
<td>Resolved</td>
<td></td>
</tr>
<tr>
<td>9/58</td>
<td>54</td>
<td>AN</td>
<td>Hypertension</td>
<td></td>
<td>2 months</td>
<td>Headache, TVO</td>
<td>Diamox</td>
<td>Resolved</td>
<td></td>
</tr>
<tr>
<td>10/53</td>
<td>25</td>
<td>AN</td>
<td>+</td>
<td>Heavy smoker</td>
<td>2 months</td>
<td>Headache, blurred vision, +</td>
<td>Prednisone</td>
<td>Optic atrophy</td>
<td></td>
</tr>
<tr>
<td>11/57</td>
<td>28</td>
<td>BN</td>
<td></td>
<td></td>
<td>3 months</td>
<td>Headache, TVO</td>
<td>L-P short, Prednisone</td>
<td>Optic atrophy</td>
<td></td>
</tr>
<tr>
<td>12/50</td>
<td>36</td>
<td>BN</td>
<td>Rheumatic fever</td>
<td></td>
<td>1 year</td>
<td>Headache, TVO</td>
<td>Diamox</td>
<td>Resolved</td>
<td></td>
</tr>
<tr>
<td>13/49</td>
<td>37</td>
<td>AN</td>
<td>ND</td>
<td>Hypertension</td>
<td>1 month</td>
<td>Headache</td>
<td>Prednisone</td>
<td>Resolved</td>
<td></td>
</tr>
<tr>
<td>14/39</td>
<td>33</td>
<td>AN</td>
<td>+</td>
<td></td>
<td>1 month</td>
<td>Headache, TVO</td>
<td>Prednisone</td>
<td>Optic atrophy, nasal field defect</td>
<td></td>
</tr>
<tr>
<td>15/56</td>
<td>55</td>
<td>AN</td>
<td>Hypercholesterolemia</td>
<td></td>
<td>2 months</td>
<td>TVO, Trinitas, vertigo</td>
<td>Diamox</td>
<td>Resolved</td>
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</tr>
<tr>
<td>16/22</td>
<td>17</td>
<td>AN</td>
<td>ND</td>
<td></td>
<td>2 months</td>
<td>Headache</td>
<td>Diamox</td>
<td>Resolved</td>
<td></td>
</tr>
<tr>
<td>17/22</td>
<td>21</td>
<td>AN</td>
<td>ND</td>
<td></td>
<td>3 months</td>
<td>TVO</td>
<td>Diamox</td>
<td>Resolved</td>
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<tr>
<td>18/35</td>
<td>30</td>
<td>AN</td>
<td>ND</td>
<td></td>
<td>3 months</td>
<td>TVO</td>
<td>Diamox</td>
<td>Resolved</td>
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</tr>
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</table>

AN, after 1980; BN, before 1990; Diamox® (ESI Lederle Generics, Philadelphia, PA), acetazolamide; L-P, lumbo-peritoneal; ND, no data; Neptazane® (ESI Lederle Generics, Philadelphia, PA), methazolamide; TVO, transient visual obscurations.

(nine with hypothyroidism, five with polycystic ovaries, two with hyperprolactinemia, and one with hGH deficiency). No hormonal aberrations were recorded in our male patients. There was no difference in the sexes regarding clinical presentation, response to drug treatment, and outcome.

The present results should be regarded with some caution. The obesity data lacked standardization concerning height, weight, and body frame, as well as age and gender. Thus, it was not possible to compare our data to those available on a small sample of the adult Israeli population for which morphometric data were recently recorded. The possibility that women may be more anxious and therefore overutilize health services—thus receiving the diagnosis of PTC more frequently—could be ruled out by the finding that the diagnostic delay in females was not significantly different from that in males.

Our results seem to suggest that SVT should be seriously considered, particularly in men presenting with PTC. The presence of PTC in lean or normal-weight males, with no evidence of hormonal dysfunction, is intriguing and might indicate that risk factors other than being overweight play a role in causing idiopathic intracranial hypertension in such patients.

We recommend routine use of contrast-enhanced MR/MRV for the diagnosis of PTC. A search for endocrinopathies indicated in females may not be beneficial in males.

REFERENCES

Reversible Blindness Resulting From Optic Chiasmitis Secondary to Systemic Lupus Erythematosus

Larry P. Frohman, MD, Brett J. Frieman, DO, and Leo Wolansky, MD

Objective: To report the diagnosis, radiologic findings, and therapy of a 51-year-old female with systemic lupus erythematosus (SLE) who, while on hydroxychloroquine maintenance therapy, presented with a junctional scotoma indicative of chiasmal disease. This visual loss developed after she had been tapered off corticosteroids.

Materials and Methods: An interventional case report of a female that was given acute therapy with 1-gram daily of intravenous methylprednisolone sodium succinate for 5 days, followed by maintenance methotrexate and a slow taper of oral prednisone. Magnetic resonance imaging (MRI) scans, visual acuity, color vision, and threshold visual fields were performed.

Results: The MRI scan showed chiasmal involvement, which may occur in SLE in absence of any other evidence of systemic activity. Therapy led to visual function returning to 20/20 OD and 20/20 OS, with normal Ishihara plates OU and only minimal paracentral depressions OU. She has been able to be weaned off prednisone while on methotrexate maintenance.

Conclusions: Chiasmal involvement may occur in SLE in absence of any other evidence of systemic activity. Maintenance with hydroxychloroquine may not be adequate to prevent this rare cause of visual loss in SLE. Aggressive therapy of chiasmal involvement in SLE, even when the visual loss is profound, may lead to visual restoration, which was virtually complete in this case. Methotrexate may be an alternate agent for patients who break through with optic neuropathy while on hydroxychloroquine.

Systemic lupus erythematosus (SLE) is an autoimmune disorder that commonly affects the skin, musculoskeletal system, renal system, and, less commonly, the central nervous system and visual system. Most visual complaints from SLE result from retinopathy and anterior uveitis (1); optic neuropathy occurs less often. We report a unique case of a patient with SLE whose only manifestation of disease activity was chiasmal and posterior optic nerve inflammation confirmed by magnetic resonance imaging. Additionally, the patient’s symptoms occurred while she had been taking 400 mg of hydroxychloroquine daily. Following high-dose corticosteroids, the patient had recovery of vision.

CASE REPORT

A 51-year-old female was referred to the neuroophthalmologist on June 11, 1996, to be monitored for signs of hydroxychloroquine-induced retinal toxicity. She had a 26-year history of SLE that was diagnosed after she developed a malar rash, arthritis, and mild renal changes; she also had elevated titer of anticardiolipin antibody of IgM idiotype. She was taking chlorthalidone, levothyroxine, estradiol, medroxyprogesterone, and baby aspirin at the time of presentation.

Her ocular history was significant for two bouts of optic neuritis (OU in 1990 and OD in 1994) with complete recovery of vision. She also had a retinal pigment epithelial detachment OD in 1990. The patient was taking 400 mg of hydroxychloroquine daily and had been on a tapering dose of prednisone (at presentation to us, 5 mg and 2.5 mg on alternate days) since the second bout of optic neuritis. The initial neuro-ophthalmology examination (2 years before the chiasmal involvement) showed best-corrected acuity of 20/25 OD and 20/20 OS. Ishihara color plates were 5.5/6 correct OU. The pupillary reactions were normal. The slit lamp exam, intraocular pressure, and ocular rotations were normal. She had 1 mm of ptosis OS with good levator function (present since 1992). The central 24-degree threshold field OD was normal centrally with some mild general constriction worse nasally. The field OS was normal except for some mild general peripheral constriction. Despite the prior history, the discs were pink, sharp, with a cup to disc ratio of 0.1 OU. The vessels and periphery were normal. There was residuum of a retinal pigment epithelial detachment along the superotemporal arcade OD. The retina was otherwise normal. She was followed and was stable for 2 years. Her rheumatologist weaned her off prednisone in early June 1998 after improvement of
FIG. 1. A: Axial Short TI (tau) Inversion Recovery (STIR) image (repetition time [TR] 3500, TI (tau) 165, echo time [TE] 75). B: Oblique axial reformatted volume acquisition T2-weighted image. C: Coronal T2-weighted image (TR 4000, TE 75). D: Axial post-contrast T1-weighted images (TR 600, TE 22). E: Coronal post-contrast T1-weighted images (TR 600, TE 26). On the long TR images, abnormal hyperintensity is seen in the optic chiasm, tracts, and nerves (black arrowheads in A, B, and C) in comparison to the normal signal seen in the cerebral white matter (A). There is a striking size difference of the spared, hypointense, intraorbital segments of the optic nerves (white arrows in A and B) in comparison to the edematous cisternal segments (black arrowheads in A and B). Also noted is relative sparing of the inferior surface of the cisternal segment bilaterally (C). Postcontrast, there is extensive enhancement of the chiasm and nerves (arrowheads in D and E).
her arthralgias. She remained on 400 mg of hydroxychloroquine daily.

On July 8, 1998, 1 month after discontinuing corticosteroids, she was seen emergently for bilateral painless visual loss that she had noted for 2 weeks. Upon examination, the patient was light perception with projection OD and 20/70 OS. Color plates were 0/6 in the left. The right pupil barely reacted to light at 6 mm; the left was 6 mm. A right afferent pupillary defect was present. Extraocular movements were full. The slit lamp examination was unremarkable, and the intraocular pressures were 14 OU. The visual field OS showed a nearly complete temporal hemifield defect (e.g., a junctional scotoma was present). The fundus examination did not show any new changes except for mild temporal pallor of the disc OD. The cranial nerve examination was normal as was the rest of the neurologic exam. The patient was admitted for treatment with intravenous steroids and further work-up. She was started on a 5-day course of 1 g of intravenous methylprednisolone. The day after admission, her visual acuity declined to light perception OD and 20/80 OS.

Laboratory results included a complete blood count that showed an elevated white blood count at 13.1 T/μL (normal 4.5–11.0 T/μL). Chemistry 12 panel showed only an elevated glucose of 201 mg/dL (normal 70–109 mg/dL). Thyroid function test, prothrombin time, activated partial thromboplastin time, and urinalysis were all within normal limits. IgG was 1700 mg/dL (normal 691–1618 mg/dL) and IgM was 334 mg/dL (normal 60–265 mg/dL). Complement 3 was 76 mg/dL (normal 88–201 mg/dL), whereas complement 4 was 18.7 mg/mL (normal 15.7–47.2 mg/mL). C-reactive protein was negative. Vitamin B₁₂ was 964 pg/mL (normal 190–1060 pg/mL). Antinuclear antibody screen was positive with a titer greater than 1:640 (negative 1:40). Anti-double-stranded DNA was negative with a titer of 1 to 10. Varicella IgG was positive. Epstein–Barr virus IgG was positive, whereas IgM was negative. Lyme titer was also negative. MRI showed a diffuse thickening, edema, and enhancement of the optic chiasm, tracts, and cisternal segments of the optic nerves (Fig. 1).

Lumbar puncture was performed, the cerebrospinal fluid (CSF) was clear. CSF glucose was 84 mg/dL (normal 40–80 mg/dL), and the CSF protein was 74 mg/mL (normal 15–45 mg/mL). The red and white cell counts were normal and the Veneral Disease Research Laboratory (VDRL) was nonreactive. Gram stain and all cultures were negative. She was discharged on 80 mg of oral prednisone daily and 15 mg of methotrexate weekly.

One week later, her vision improved to 20/800 OD and 20/80 OS, and the visual field OS improved to show a cecocentral scotoma. Two weeks after discharge, a slow prednisone taper was begun. By 1 month after discharge, her vision improved to 20/25 OD and 20/20 OS, and her color vision had also improved to 1/6 OD and 4/5/6 OS. Her right visual field showed a central and paracentral depression and a couple of scattered islands of depression. The OS was normal with the exception of diminished color vision. She was removed from prednisone 13 months after discharge. At last follow-up examination in January 2001, she was on methotrexate (15 mg each week), calcitonin, estradiol, medroxyprogesterone, baby aspirin, and 400 mg of hydroxychloroquine. Her visual acuity was 20/20 OD and 20/20 OS. Ishihara color plates were 100% correct OU. She no longer had a relative afferent pupillary defect. She had mild temporal disc pallor OU. Her threshold visual field had minimal paracentral depression OU. She has not had any further manifestations of her lupus.

**DISCUSSION**

Upon review of the literature, two reports mention patients with SLE and chiasmal involvement. Sklar et al. (2) mention a case of SLE involving the optic chiasm but did not present details of the case. They discussed the benefits of MRI with gadopentetate dimeglumine and fat suppression to detect optic neuropathy. Jabs et al. (3) report data of a patient with retrobulbar optic neuropathy and chiasmal syndrome that occurred with a systemic flare of SLE. We have previously reported a case of chiasmitis with swollen chiasm demonstrated on metrizamide cisternogram in a patient with autoimmune optic neuropathy, an illness where patients may have some features of SLE but do not meet clinical criteria for its diagnosis (4). To the authors’ knowledge, this article is the first case report of a patient where chiasmal involvement in SLE occurred without other active systemic manifestations of SLE.

The many ocular manifestations of SLE include retinopathy, anterior ischemic optic neuropathy, retrobulbar ischemic optic neuropathy, papillitis, or retrobulbar neuritis (1,3). These presentations of SLE are rare and are not included in the criteria for classification of SLE established by the American Rheumatoid Association (5). Based on the patient’s prior symptoms, she fit the criteria for, and was diagnosed with, SLE before the development of optic neuropathy (6). After other causes were ruled out, SLE was determined to be the cause of her chiasmal optic neuritis. SLE is believed to be caused by an autoimmune-induced vaso-oblusion occurring in small vessels (3,7). The inflammatory response may result from the presence of antiphospholipid antibodies that are often found in patients with SLE; alternately, these antibodies may be a marker for disease activity (8). Hydroxychloroquine did not protect our patient against a flare of SLE, such as optic neuropathy, occurs in a patient on hydroxychloroquine (10).
REFERENCES


A 42-year-old male presented with acute onset of an inferior visual field defect OD after sildenafil citrate use. Examination revealed a right relative afferent pupilary defect and a swollen disc with a 0.1 cup-to-disc ratio and a prominent disc hemorrhage. Anterior ischemic optic neuropathy (AION) is associated with acute episodes of hypotension in patients with structurally crowded discs. Sildenafil citrate may cause episodes of hypotension and was temporally related to the onset of symptoms in this patient. Because patients are often reluctant to volunteer their history of sildenafil citrate use, the physician may need to ask specifically about use of this medication. Physicians should counsel patients with crowded optic discs and a history of nonarteritic anterior ischemic optic neuropathy in one eye that use of sildenafil citrate might increase their risk of ischemic optic neuropathy in the fellow eye.

**Key Words:** Viagra—Sildenafil citrate—Anterior ischemic optic neuropathy—Crowded discs—Hypotension—Neuropathy.

Studies have shown therapeutic doses of sildenafil (25–100 mg) reduce mean peak systolic and diastolic blood pressures by approximately 10 mm Hg (1). The male examined developed anterior ischemic optic neuropathy (AION) less than 24 hours after taking a dose (50 mg) of sildenafil citrate (Viagra; Pfizer US Pharmaceutical Group, New York, NY). We believe this case supports a possible association between the use of sildenafil citrate and AION. The rationale for this association is supported in our review of the pathophysiology of AION and the mechanism of action of sildenafil citrate.

**CASE REPORT**

A 42-year-old male with a history of depression and sexual dysfunction began taking sildenafil citrate (50 mg). The first dose was taken without adverse effect. One week later, he took a second dose. Twelve hours later, he noted the onset of an aching sensation behind the right eye that was exacerbated with eye movement. No discomfort was noted on the left. The following night, he took a third dose; the next morning, he noted blurred vision OD, which he described as dimness of the entire inferior half of his visual field. Ophthalmologic examination revealed a right-sided relative afferent pupillary defect and swelling of the right optic disc superiorly, suggesting a right-sided optic neuropathy. The patient was then referred to us for neuro-ophthalmologic evaluation.

The patient's past medical history was significant only for depression and sexual dysfunction. He had no history of hypertension or hypotension. The patient's only medication other than sildenafil was sertraline for depression. Before this event, he had no history of ocular disease except for a congenital color vision deficiency. His family history showed no optic nerve problems or sudden blindness. His wife, a nurse, had positive results from a purified protein derivative (PPD) skin test. Review of systems was noncontributory.

Initial neuro-ophthalmologic examination revealed a best corrected visual acuity of 20/20 OU. Color vision testing with Hardy-Rand-Rittler (HRR) plates revealed only 7 of 10 correct OU. Automated visual fields (Humphrey 30-2) revealed a dense, inferior, altitudinal defect as well as a superior arcuate-type defect in the right eye (Fig. 1). Central vision above the midline was spared. The visual field OS was normal. Pupils were briskly reactive with a right-sided relative afferent pupillary defect. There was no proptosis. Ocular motility was normal. Biomicroscopy of the anterior segment was unremarkable. Intraocular pressures were 15 mm OU. Dilated fundus exam OD revealed prominent swelling of the superior aspect of the disc with a disc rim hemorrhage (Fig. 2). Funduscopy of the left eye revealed a healthy appearing, but crowded, disc with a cup-to-disc ratio of 0.1. The vessels, macula, and peripheral retina were normal OU.

Although the funduscopic picture was most consistent with AION, we also considered the possibility of an
inflammatory optic neuropathy (optic neuritis), because the patient reported pain with eye movement. We, therefore, initiated an evaluation for possible inflammatory causes. Laboratory testing revealed a normal antinuclear antibody titer, an erythrocyte sedimentation rate of 10, a normal complete blood count, a nonreactive fluorescent treponemal antibody absorption test, and a normal tuberculin skin test. A chest radiograph was unremarkable. A magnetic resonance image (MRI) scan of the brain with gadolinium and fat suppression demonstrated optic nerves that appeared normal and no white matter lesions suggestive of demyelinating disease.

The absence of any evidence of a systemic inflammatory disorder, and the presence of structurally crowded discs, led us to conclude that the patient had experienced an episode of AION rather than an inflammatory optic neuropathy. The patient was counseled to discontinue using sildenafil citrate and to monitor his blood pressure regularly. No other treatment was initiated. The patient noted a step-wise progression of visual loss OD for three weeks after the initial episode. Repeat visual fields at 1 month showed diffuse depression with loss of the central island of vision (Fig. 3). The visual acuity at last follow-up evaluation, 1 year after initial presentation, was 20/200 OD and 20/20 OS. The disc swelling and hemorrhage had resolved with residual superior optic atrophy (Fig. 4).

FIG. 1. Humphrey 30-2 visual field OS and OD upon initial examination.

FIG. 2. Fundus photo A: OD and B: OS upon initial examination.

DISCUSSION

The pathophysiology of AION is poorly understood and remains the focus of considerable debate (2). Hayreh (3) suggested that the problem is localized to the posterior ciliary arteries in the disc and the retrolaminar area. He demonstrated that occluding the posterior ciliary arteries in monkeys causes infarction of the retrolaminar and laminar portions of the optic nerve. Axoplasmic flow is consequently reduced and disc swelling results (4). Hayreh later demonstrated that complete occlusion of the posterior ciliary arteries is not essential to produce AION. In 1970, he showed that the circulation in the optic disc, peripapillary choroid, and choroid is dependent upon the difference between the intraocular pressure and perfusion pressure in the posterior ciliary arteries. When an imbalance results, as in a sudden and marked systemic arterial hypotension, AION may result. Hayreh (5) also suggested that nocturnal hypotension may be an important precipitating factor in the pathophysiology of AION. He demonstrated through 24-hour ambulatory blood pressure monitoring that nocturnal hypotension may act as the final insult leading to ischemia and AION in optic nerves that have been rendered vulnerable to ischemia by predisposing factors. Clinical support for the role of nocturnal hypotension in triggering AION comes from other studies done by Hayreh (6) that found that 73.3% of patients with AION noticed their visual loss upon awakening, either in the morning or from a nap.

Hoyt (7) was the first researcher to note that some discs have certain anatomic features that seem to predispose them to AION. Burde (8) coined the term "disc at risk" to describe these structurally crowded discs characterized by a small nerve head with a small or absent physiologic cup, abnormal branching of the central vessels, and full nerve fiber bundles obscuring the disc margin.

The patient described in this report had optic discs with the structural anatomy described as disc at risk. His initial presentation was characteristic of AION with disc
swelling and nerve fiber layer hemorrhages and subsequent optic atrophy. The altitudinal nature of his initial visual field defect was also typical for AION. His progressive visual field defect over time is a well-recognized phenomenon seen in as many as 29% of eyes during the first month after the initial event (9).

The retrobulbar pain with eye movement, although more suggestive of inflammatory optic neuropathy, is reported by 10% of patients with AION (10). Our laboratory evaluation revealed no evidence of an underlying autoimmune process, vasculitis, or infection. The initial disc appearance, absence of subsequent improvement in visual function, and eventual profound optic atrophy would be atypical for demyelinating optic neuritis. Furthermore, the patient had no history of neurologic symptoms or MRI lesions to suggest systemic demyelinating disease. For all of these reasons, we are confident that our patient had an ischemic, rather than inflammatory, optic neuropathy.

Sildenafil citrate is the first of a new group of oral agents approved for managing male erectile dysfunction that acts directly on the penile vasculature (11). During sexual stimulation, the cavernous nerves release nitric oxide (NO), which induces cyclic guanosine monophosphate (cGMP) formation and leads to smooth muscle relaxation and increased blood flow to the corpus cavernosum. The result is an erection (12). Phosphodiesterase type 5 (PDE5) is a naturally occurring enzyme, found in high concentrations in the corporis cavernosum, that breaks down cGMP. Sildenafil citrate selectively inhibits PDE5, thus blocking the breakdown of cGMP and facilitating the erectile process (13). The NO-cGMP pathway also plays an important role in modulating systemic blood pressure through its effect on basal vascular tone.

We believe that sildenafil citrate may have contributed to the episode of AION in our patient. The sildenafil citrate may have accentuated his physiologic nocturnal hypotension enough to decrease the perfusion pressure in the posterior ciliary arteries. This effect resulted in ischemia in a disc that was already predisposed to AION by the anatomic disc-at-risk configuration. The temporal relationship between the doses of sildenafil citrate and the onset of visual loss make it difficult to accept the notion that these were unrelated coincidental events.

To date, there has been only one other published case report temporally linking an episode of AION to sildenafil citrate (14). We are aware of two similar cases of anterior ischemic optic neuropathy related to sildenafil citrate use (oral communication with Howard Pomeranz, MD). We also examined another patient who reported sildenafil citrate use the night before experiencing acute visual loss in one eye from AION. However, the patient, a 60-year-old male, had experienced a previous episode of AION in the fellow eye several months before his first dose of sildenafil citrate. He, like our reported patient, had bilateral disc-at-risk anatomy.

We suggest that a complete review of medications, including specific questions about sildenafil citrate use, is essential in the evaluation of patients with signs and symptoms of AION. Some patients may be reluctant to volunteer information about their use of sildenafil citrate because of the stigma associated with erectile dysfunction. Our patient, for example, did not inform us about his sildenafil citrate use until his wife was absent on one of the follow-up visits. We believe sildenafil citrate is relatively contraindicated in patients with a history of AION. In addition, it may be reasonable to counsel patients with bilateral disc-at-risk anatomy to be cautious about using sildenafil citrate or any other medication that might cause hypotension.

REFERENCES


FIG. 3. Repeat Humphrey 30-2 visual field OD at 1-month follow-up evaluation.

FIG. 4. Fundus photo OD at 1-month follow-up evaluation.
AION ASSOCIATED WITH VIAGRA


A Girl Without a Chiasm: Electrophysiologic and MRI Evidence for the Absence of Crossing Optic Nerve Fibers in a Girl With a Congenital Nystagmus

Nomdo M. Jansonius, MD, PhD, Ton (A) M. van der Vliet, MD, Frans W. Cornelissen, PhD, Jan Willem R. Pott, MD, PhD, and Aart C. Kooijman, PhD

An otherwise healthy 15-year-old girl with a congenital nystagmus was evaluated at our department using visual evoked potential recording and magnetic resonance imaging. She appears to have the unique isolated inborn absence of the optic chiasm, described only once before in two unrelated girls. Unlike these previously described cases, our patient does not seem to display a see-saw nystagmus.

Key Words: Optic chiasm—Congenital nystagmus—See-saw nystagmus—Achiasmatic—Albino.

When a nystagmus is recognized shortly after birth, the first concern is the differentiation between a primary congenital nystagmus (motor defect nystagmus) and a nystagmus secondary to a bilateral afferent defect (sensory defect nystagmus). We present a patient with a congenital nystagmus, originally classified as a motor defect nystagmus. Fifteen years after birth, the diagnosis had to be reconsidered because of an extremely rare magnetic resonance imaging (MRI) finding.

CASE REPORT

An otherwise healthy girl was diagnosed with a congenital nystagmus 4 months after birth. She did not have any other ocular or neurologic abnormality, and the family history was negative. The first measurement of visual acuity, at an age of 3 years, yielded values of 20/100 OD and 20/200 OS. Acuity remained apparently stable in the first decade. A combined myopic astigmatism developed gradually.

At the age of 15 years, she returned to our department. Acuity at that time was 20/400 OD (-3.50-2.00x10°) and less than 1/60 OS (-6.00-4.00x20°). She had not noticed any acuity change herself. She was evaluated along with her 10-year-old sister, who complained of poor vision for the past year. In this girl, acuity measurement yielded 20/100 OU (previously documented to be 20/20). Both girls performed well in a regular secondary school, the elder with ambulant support of a low-vision rehabilitation service. In both girls, perimetry, electroretinogram (ERG), visual evoked potential (VEP), extensive blood investigations, a neurologic examination, and a MRI were performed in addition to a thorough ophthalmic examination. In the younger of the two sisters, no abnormalities were found, except for concentrically constricted visual fields. She was diagnosed to have functional visual loss. Currently (2 years later), her visual acuity is at least 20/25.

In the elder sister, ophthalmic examination showed a horizontal nystagmus that remained horizontal in upgaze and downgaze, normal pupillary reactions without a relative afferent defect, no iris transillumination, and a normal fovea and optic nerve head. Fundus examination and photography were hampered by photophobia. No substantial esotropia or exotropia was found. Versions were normal. Prism tests (base-out prisms for testing the presence of binocular single vision) were inconclusive because of the nystagmus.

Perimetry revealed concentrically constricted visual fields, symmetrically around and without any discontinuity along the vertical meridian. Figure 1 presents the results. This finding was reproduced at a separate visit. MRI revealed a complete absence of the chiasm; the optic nerves appeared to be headed directly toward the geniculate bodies. There were no signs of a septo-optic dysplasia (Figs. 2 and 3). This unusual finding has been described only once before (1,2).

Eye movement registrations performed in primary gaze are shown in Figure 4. As the figure shows, the nystagmus is essentially a horizontal pendular nystagmus with a frequency of approximately 2 to 3 Hz and an amplitude of approximately 10°. Unlike the previously described cases, our patient did not seem to display a see-saw nystagmus.
Both ERG and VEP were recorded. ERG responses were strictly normal. Pattern VEP did not provide consistent recordings. Flash VEP, when tested monocularly, yielded a response after approximately 150 to 200 ms, only in the hemisphere on the side of the stimulated eye. This result is shown in Figure 5.

Visual evoked potential asymmetry has been measured (1,2) in both patients with albinism (contralateral response exceeds ipsilateral response) and in achiasmatic patients (ipsilateral response exceeds contralateral response). We analyzed our VEP data using a method modified from Ver Hoeve et al. (unpublished; presented at the 1998 meeting of the American Association for Pediatric Ophthalmology and Strabismus, Palm Springs, CA) and Soong et al. (3), who studied misrouting in albinism. In short, a chiasm coefficient is calculated from the differences of the recorded signals from the right and left hemispheres. For details, see Table 1. The chiasm coefficient is a number between -1 and 1. In case of a normal chiasm, the chiasm coefficient is approximately zero. This result also holds if one optic nerve produces a weaker signal than the contralateral one. If a weaker signal is recorded on one hemisphere than on the other, a positive coefficient results. A negative chiasm coefficient is consistent with either >50% crossing of fibers in the chiasm (as in albinism) (4) or with <50% crossing (as in an achiasmatic visual system). If noise dominates the recorded signal, the chiasm coefficient will tend toward zero. We determined the chiasm coefficient 13 times in our patient from measurements obtained during two separate visits. Values ranged from -0.89 to -0.35. In six subjects with a presumed normal chiasm, we found values ranging from -0.2 to 0.9. In five albino patients studied, the chiasm coefficient varied between -1.0 and 0.

DISCUSSION

In this article, we presented an unusual finding in a 15-year-old girl with a congenital nystagmus. The isolated absence of the optic chiasm we found is, to our knowledge, the first independent confirmation of Apkarians nondecussating retinal-fugal fiber syndrome, originally described in two unrelated girls (1,2). Absence or hypoplasia of the chiasm has been described in patients (male and female) with several other midline abnormalities (5). Like the previously published isolated cases, our patient displays a reduced visual acuity OU, a congenital nystagmus, no iris transillumination, and no foveal hypoplasia. Like the others, she has blue irides and blond hair. Blue eyes and blond hair, however, is the default for girls in the Netherlands, and all three girls are Dutch. Unlike the previous findings (1,5), our patient does not seem to show a see-saw nystagmus.

It must be noted that when recording such a large horizontal nystagmus, a small vertical nystagmus can easily be overlooked. Also, a small vertical nystagmus that is phase locked with the horizontal nystagmus can easily be induced as an artefact. The apparent presence or...
absence of a vertical nystagmus depends on the definition of the horizontal plane. Changing the horizontal plane a few degrees makes it possible to observe a conjugate vertical nystagmus, a disconjugate nystagmus (SSN), or no vertical nystagmus at all. Because of this we can not exclude that there is some vertical conjugate nystagmus or SSN, but the nystagmus of our patient appears to have at least a remarkably small vertical component as compared to the previously published data in which the vertical amplitude seems to exceed the horizontal amplitude (2).

In addition to the achiasmatic humans, a congenital absence of the chiasm has been described in Belgian sheepdogs (6). The achiasmatic dogs do present a horizontal nystagmus, and at least some of them also have a see-saw nystagmus (7,8).

![FIG. 4. Eye movement recordings. Recordings OD and OS, horizontally and vertically, were all performed simultaneously. Eye movements were registered using an EyeLink Gaze tracker (Sensomotoric Instruments, Teltow, Germany). The EyeLink is an infrared video-based pupil tracker that samples eye position 250 times per second. It is equipped with head position compensation—although this feature was not critical in our experiment, because we used a chinrest. Technically, the EyeLink's spatial resolution is better than 0.1 degrees. Eye-position accuracy with a chinrest, in healthy subjects, is typically approximately 0.5 degrees average error (measured by calibration-accuracy validation). Because of the large nystagmus in our subject, the EyeLink’s normal automated calibration procedure failed and was replaced by a manual posthoc procedure: the subject had to look at four different positions (left, right, above, and below the central fixation point), and the signals obtained by this procedure were used to scale the horizontal and vertical eye-movement traces.](image-url)

![FIG. 5. Flash VEP recordings. Stimulus is given at t = 0 ms. Offset is set to 5, 15, 25, and 35 μV, respectively. Electrode position was 3 cm above and lateral with respect to the inion. Reference electrode was at the ipsilateral ear; common at the forehead. RH-OD is the signal recorded from the right hemisphere while stimulating OD; LH-OD the signal from the left hemisphere while stimulating OD; RH-OS the signal from the right hemisphere while stimulating OS; and LH-OS the signal from the left hemisphere while stimulating OS.](image-url)
A GIRL WITHOUT A CHIASM

TABLE 1. Calculation of the chiasm coefficient

To cope with drift and offset, the calculation starts with a high-pass filtering of the recorded signal. This filtering is established by subtracting the average of the previous \( t \) ms of the recorded signal from the recorded signal:

\[
V(t) = V_r(t) - \left( \frac{1}{T} \int_{t'=-\infty}^{t'} V_r(t') dt' \right)
\]

where \( V_r(t) \) is the filtered signal and \( V_r(t) \) the recorded signal. Calculations were performed with \( T = 60 \) ms. Subsequently the chiasm coefficient (cc) is calculated:

\[
cc = \frac{\int \left( [V_{RH,OD} - V_{LH,OD}] \cdot [V_{RH,OS} - V_{LH,OS}] \right) dt}{\int \left( [V_{RH,OD} - V_{LH,OD}] \cdot [V_{RH,OS} - V_{LH,OS}] \right) dt}
\]

where \( V_{RH,OD} \) is the signal recorded from the right hemisphere while stimulating OD, \( V_{LH,OD} \) the signal from the left hemisphere while stimulating OD, \( V_{RH,OS} \) the signal from the right hemisphere while stimulating OS, and \( V_{LH,OS} \) the signal from the left hemisphere while stimulating OS. Calculations were performed with \( t_1 = 60 \) ms and \( t_2 = 300 \) ms; stimulus is given at \( t = 0 \) ms.

In dogs, achiasmatism has an autosomal recessive mode of inheritance (6). In humans, only unrelated cases of achiasmatism have been described. Our patient has an unaffected brother and sister. One of the patients described by Apkarian (2) is a fraternal twin (both girls) and has an unaffected twin sister and an unaffected older brother and sister. Five normal brothers and sisters do not exclude an autosomal recessive mode of inheritance (\( p = 0.29 \), Poisson distribution with 0 observed and \( 5/4 = 1.25 \) expected). An autosomal dominant mode of inheritance could be considered less likely because of the absence of either nystagmus or visual impairment in the family history. Three female and no male patients with isolated achiasmatism makes an X-linked mode of inheritance less likely and suggests that achiasmatism affects women more frequently than men. However, this difference is not significant (\( p = 0.13 \), Poisson distribution with 3 observed and \( 3/2 = 1.5 \) expected).

Finally, achiasmatism found at age 15 can be a true agenesis or a secondary degeneration. In our case, perimetry provides a major argument against a degeneration. A degeneration of the chiasm should yield a bitemporal hemianopsia. Visual fields symmetrically around and without any discontinuity along the vertical meridian, as found in our patient, suggest a true agenesis. Comparable visual fields were found by Apkarian et al. (1).

REFERENCES

Autoenucleation of a Blind Eye

Jason S. Dilly, MD, and Richard K. Imes, MD

Autoenucleation has been reported sporadically in ophthalmic and psychiatric literature. Individuals who attempt to blind themselves are usually psychotic and often have a history of substance abuse. Sexual and religious delusions are common. All previous reports of autoenucleation have, to our knowledge, involved sighted eyes. We report the case of a man who digitally removed his blind OS, resulting in complete temporal hemianopia in his remaining eye from chiasmal injury.

CASE REPORT

A 54-year-old man with a medical history of paranoid schizophrenia was found sitting in a chair with an intact globe lying on the floor next to him. His hands were blood soaked, his OS lids were swollen, and he was bleeding from a left lower eyelid laceration.

In the emergency room, the orbit was lavaged with antibiotic solution, the lower eyelid laceration was repaired, and a pressure dressing was applied. Examination of the patient's OD revealed a complete temporal hemianopia. He was admitted to the hospital and started on intravenous antibiotics and haloperidol. The patient said his eye was "evil and had to come out." He had stopped taking his psychiatric medications several weeks before removing the eye. Nine years before this episode, he had attempted to remove this eye with his fingers, causing a scleral rupture, retinal detachment, and dislocated lens. The eye was blind thereafter.

Gross examination of the globe showed attached, but torn, extraocular muscles and an attached segment of optic nerve measuring 59 mm in length (Fig. 1). Histopathologic examination of the globe and nerve showed retinal detachment, dislocated lens, and complete atrophy of the optic nerve. There was no evidence of chronic intraocular inflammation, glaucomatous cupping of the disc, or rubeosis of the iris. Magnetic resonance imaging showed absence of the left globe, left optic nerve, and left half of the optic chiasm (Fig. 2).

DISCUSSION

In 1984, Krauss et al. (1) reported a case of autoenucleation and reviewed the medical literature. They found previous reports of 19 cases of bilateral autoenucleation and 31 cases of unilateral autoenucleation. The point at which the optic nerve was severed was reported in 18 eyes. In two cases, the nerve was severed at or near the globe. In 10 cases, the nerve was severed between 15 mm and 30 mm posterior to the globe. In six cases, the nerve was severed at or near the chiasm. In 7 of 31 cases of unilateral autoenucleation, a temporal hemianopia was found in the remaining eye.

In 1996, Arkin et al. (2) reported the case of a 25-year-old man who enucleated his OS with his fingers, removing the globe and 46 mm of attached optic nerve. An incomplete temporal hemianopia was recorded OD. Magnetic resonance imaging showed absence of the left
optic nerve and asymmetry of the anterior chiasm. Our case showed absence of the left half of the chiasm and a complete temporal hemianopia OD.

Sin, guilt, and atonement are common themes in cases of autoenucleation. Many patients are religiously preoccupied and refer to the bible verse St. Matthew 5:29, which says: “And if thy right eye offend thee, pluck it out, and cast it from thee; for it is profitable for thee that one of thy members should perish, and not that thy whole body should be cast into hell.” Ferenczi (3) interprets autoenucleation as self-castration. One of two patients reported by MacLean and Robertson (4) in 1976 removed his OS with his fingers after finding no suitable instrument to remove his genitalia. In 1976, Wolff, Wright, and Walsh (5) described a 24-year-old man who attempted to remove his OS after attempting to sever his penis. Menninger (6) suggests that autoenucleation is focal suicide; however, we would not characterize our patient’s removal of his already blind or “dead” eye as focal suicide.

Our case demonstrates that vision is not essential to provoke a psychotic patient to remove an eye.

REFERENCES
Rapid Recovery With Oral Zinc Sulphate in Deferoxamine-induced Presumed Optic Neuropathy and Hearing Loss

Antonio Pinna, MD, PhD, Laura Corda, MD, and Francesco Carta, MD

Deferoxamine continues to be the mainstay of therapy to remove excess iron in patients requiring long-term transfusions. Overall, deferoxamine has been regarded as having minimal side effects. However, neurotoxicity-related abnormalities, such as optic neuropathy and sensorineural hearing loss, have been described in patients receiving long-term high-dose subcutaneous deferoxamine (1–3). Management of deferoxamine toxicity consists of immediate drug withdrawal. Reversal of toxicity takes weeks to months and does not appear to be related to the deferoxamine dosage and the patient’s age. We report a case of deferoxamine-induced presumed optic neuropathy and sensorineural hearing loss. The patient recovered rapidly after treatment with oral zinc sulphate.

CASE REPORT

A 25-year-old woman with homozygous beta-thalassemia presented with visual loss lasting 2 weeks. She had been regularly transfused since the age of five. Pretransfusional Hb had been maintained in the 11 to 13 g/dL range in the previous 2 years. She had been taking subcutaneous deferoxamine 2 g/d (50 mg/kg), 7 days a week, for 3 years in an attempt to achieve a negative iron balance. She has also had mild posttransfusional hepatitis C virus (HCV) chronic hepatitis. On initial examination, her best-corrected visual acuity was 20/60 bilaterally. No lens opacities were detected. Fundus examination and fluorescein angiography results were normal OU. The Farnsworth Panel D-15 test showed an irregular pattern of errors. Automated perimetry revealed bilateral central scotoma. Serum ferritin was 656 ng/mL (normal range: 9–120 ng/mL), serum iron was 191 µg/dL (normal range: 40–160 µg/dL), serum calcium was 4.12 mEq/L (normal range: 4.5–5.5 mEq/L), serum magnesium was 1.6 mg/dL (normal range: 1.8–2.5 mg/dL), and serum copper was 106 µg/dL (normal range: 70–140 µg/dL). Audiometry showed high-frequency sensorineural deficit bilaterally. MRI of the brain and optic nerves was normal. Apart from visual and auditory abnormalities, neurologic examination findings were normal. On the basis of these data, the diagnosis of deferoxamine-induced presumed optic neuropathy and sensorineural hearing loss was made. As a result, deferoxamine was stopped, and oral zinc sulphate (100 mg twice daily) was given. After 2 days, visual acuity was 20/20 OU, central scotomas disappeared, and color vision and audiogram abnormalities reversed completely. Pretreatment serum zinc levels were not measured, but posttreatment serum zinc was 300 µg/dL (normal range: 75–120 µg/dL). Three weeks later, the patient restarted deferoxamine 1.5 g/d, 6 days a week, and zinc sulphate was tapered to 22.5 mg twice daily. She has had no signs of ocular and auditory toxicity in the 2 years after this incident.

DISCUSSION

Generalized iron overload resulting from multiple transfusions is common in homozygous beta-thalassemia. Since 1962—when administration of intramuscular deferoxamine, a chelating agent that removes iron from ferritin, hemosiderin, and transferrin, was shown to increase urinary iron excretion substantially in patients with thalassemia (4)—determined efforts have been made worldwide to administer parenteral deferoxamine in parallel with transfusions. Overall, deferoxamine has not been associated with serious side effects and has been considered minimally toxic in patients with iron loading. Systemic toxic effects include skin flushing at the injection site, urticaria, hypotension, shock and anaphylaxis, reversible nephrotoxicity, and hearing loss. Cataract formation, retinal pigmentary degeneration, and optic neuropathy are the most substantial ocular side effects (3). Different mechanisms of possible deferoxamine toxicity include blockade of critical iron-dependent...
enzymes and reduction in critical trace elements other than \( \text{Fe}^{2+} \) (\( \text{Cu}^{2+} \), \( \text{Zn}^{2+} \), \( \text{Mg}^{2+} \), \( \text{Ca}^{2+} \)) \((1,5)\). Evidence indicates that alterations in zinc metabolism may play a role in the pathogenesis of deferoxamine neurotoxicity. Urinary zinc excretion, which is already increased in patients with homozygous beta-thalassemia, may be further increased by usual doses (50 mg/kg) of deferoxamine \((6,7)\). Oral zinc supplements with calcium diethylene triamine pentaacetic acid (Ca-DTPA) have been reported to be successful in the management of deferoxamine-induced auditory neurotoxicity \((8)\). Moreover, oral zinc sulphate may be beneficial in the management of some toxic optic neuropathies \((9)\). In our patient, a presumably toxic origin for the visual and hearing loss was suggested by the bilateral involvement. She was receiving only 50 mg/kg of deferoxamine, which is generally considered a standard and safe dose, but she had relatively low ferritin levels. It seems likely that toxic deferoxamine levels were attained because the dose was disproportionately high in relation to the amount of iron available for chelation. Similar findings have also been observed by other authors \((1)\). We are not aware of any report of toxic optic neuropathy, zinc-related or otherwise, with significant dysfunction to the levels noted, recovering completely in 48 hours. Unfortunately, we were not able to determine pretreatment serum zinc levels. However, because reversal of deferoxamine toxicity after drug withdrawal takes weeks to months, the rapid recovery of visual and auditory abnormalities in our patient suggests that excess deferoxamine may have interfered with zinc metabolism, and oral zinc supplement was beneficial. In conclusion, patients receiving deferoxamine should be closely monitored for ocular and auditory side effects. When such effects are detected, the drug should be discontinued. Oral zinc sulphate may help accelerate neurotoxicity reversal.

REFERENCES

Granulomatous Hypophysitis and Bilateral Optic Neuropathy

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A 53-year-old woman with symptoms of hypopituitarism and ophthalmoplegia was diagnosed as having idiopathic granulomatous hypophysitis and later developed bilateral optic neuritis. She responded well to steroid treatment. Granulomatous hypophysitis is a rare entity, and this is the first reported case associated with optic neuritis.

**Key Words:** Granulomatous hypophysitis—Ophthalmoplegia—Bilateral optic neuropathy.

Granulomatous hypophysitis is an rarely encountered inflammatory disorder of the pituitary gland. It is generally diagnosed as pituitary adenoma with its clinical and radiologic findings. The diagnosis is made with the observation of granulomas with epitheloid histiocytes and multinucleated giant cells that can also be associated with lymphocytes. Few cases of this entity have been reported in the literature, and its association with granulomatous disorders such as tuberculosis (1), sarcoidosis (2), histiocytosis X (3), syphilis (4) and secondary granulomatous reactions resulting from ruptured Rathke cleft cyst (5) and mucocele (6) has been documented. In the group of patients with no etiologic cause to be identified, the term idiopathic granulomatous hypophysitis is used (7).

**CASE REPORT**

A 53-year-old female was evaluated in August 1999 in another medical center because of secondary amenorrhea. Except for the noninsulin-dependent diabetes mellitus since 1985 in her history, she reported no previous illness. In her screening tests for pituitary hormone levels, decreased levels of thyroid-stimulating hormone, follicular-stimulating hormone, luteinizing hormone, and prolactin were detected. Her serum basal cortisol level was also below the normal limits. The patient was given hormone replacement therapy, including 5 mg of oral prednisolone, daily. One month later, while she was on schedule for magnetic resonance imaging (MRI), complaints of diplopia prominent on horizontal gaze, drooping of the eyelid, inward deviation, and blurring of vision OD emerged. Cranial MRI revealed a contrast-enhanced lesion with a 1.4-cm diameter consistent with pituitary macroadenoma. The patient was referred to our neurosurgery department where mild ptosis and limited abduction OD was noted. Transsphenoidal resection of the pituitary gland was planned for October 28, 1999, but an excisional biopsy was performed, and the operation was terminated after the visualization of the firm, fibrotic, and yellowish appearance of the pituitary gland. Microscopic examination disclosed preservation of anterior pituitary acini that were separated by inflammatory cell infiltrate exclusively composed of lymphocytes and plasma cells. Granulomas formed by epitheloid histiocytes and multinucleated giant cells were observed (Fig. 1). Ziehl–Nielsen staining for acid-fast bacilli, methenamine silver, and periodic acid Schiff results for fungi were negative. The histopathologic diagnosis was giant cell granulomatous hypophysitis. She received 5 days of intravenous dexamethasone therapy (4 mg every 6 hours during the postsurgical period), which was then tapered gradually and stopped in the postoperative fifteenth day. The patient was followed for a 3-month symptom-free period postoperatively.

In January 2000, 3 months after the surgery, she was first seen in the neuro-ophthalmology unit for evaluation of 15 days of progressive visual loss OD. Visual acuity was 20/400 OD and 20/20 OS with the Ishihara plates. There was a right relative afferent pupillary defect. Color vision was 0/12 OD and 12/12 OS. Visual field examination by Goldmann perimeter revealed a dense central scotoma extending to the temporal field OD and intact...
GRANULOMATOUS HYPOPHYSITIS AND BILATERAL OPTIC NEUROPATHY

FIG. 1. Granulomatous inflammation characterized by multinucleated giant cells, epithelioid histiocytes, and lymphoplasmacytic infiltration destructing the anterior pituitary gland (Hematoxylen–Eosin, × 200).

field OS. The right optic disc was swollen and the left appeared normal. Eye movements were full, there was no ptosis, and the rest of the neurologic examination was within normal limits. A recurrence of granulomatous reaction was considered in diagnosis, and she was hospitalized.

Cranial and orbital MRI revealed infundibular thickening, edema, and contrast-enhanced lesion in both optic nerves (Fig. 2). Complete blood count, erythrocyte sedimentation rate, chest X-ray, and serum biochemistry revealed no abnormalities, except for the high serum glucose level. Results for serologic markers for syphilis and serum angiotensin-converting enzyme (ACE) were found to be negative. Lumbar puncture was performed twice; cerebrospinal fluid (CSF) pressure, protein and glucose level, cytologic examination, routine bacteriologic cultures and fungal cultures, ACE level, and Venereal Disease Research Laboratory results were all within normal limits. Samples from CSF and biopsy specimen were also analyzed for specific culture for tuberculosis and detection of tuberculous bacilli with polymerase chain reaction (PCR). The protein purified derivative (PPD) test result was found to be 30 mm x 30 mm, which was regarded as positive. The patient also reported abdominal tuberculosis in her father, diagnosed 5 years ago. Visual acuity regressed to the level of light perception OD and 20/70 OS in a period of 8 days. Because of positive PPD and family history of tuberculosis, the patient began isoniazid, rifampin, ethambutol, and pyrazinamide therapy. On the fifth day of antituberculosis therapy, the vision decreased to the level of no light perception OD and 20/200 OS. Ethambutol was removed from the antituberculosis regimen because of its potential risk for optic toxicity. Taking into consideration the rapid progressive character of the symptoms and the history of benefit from increased dose of steroid therapy received perioperatively, the patient was given 1 gr/day of intravenous methylprednisolone for 5 days. Twelve hours after the onset of steroid therapy, visual acuity was 20/200 OD and 20/70 OS. On the third day of steroid therapy, visual acuity improved to 20/30 OD and 20/20 OS. Antituberculosis therapy was discontinued after PCR because the tuberculous bacilli from the CSF and biopsy specimen was found to be negative. Five days later, maintenance therapy with 1 mg/kg/day of oral methylprednisolone was initiated. On her control cranial MRI, mild regression of the previous lesions were detected. No uptake of gallium was detected in her whole body gallium-67 scintigraphy. Tuberculosis culture results were reported negative 6 weeks later. The dose of methylprednisolone was tapered gradually to 8-mg daily; she was asymptomatic, and the vision was 20/20 OU 8 months after her discharge.

DISCUSSION

Inflammatory lesions of the pituitary gland, which generally present as hypopituitarism clinically and sella turcica enlargement radiologically, are rare entities. As in our case, these entities are generally misdiagnosed as pituitary adenoma.

Two main types of inflammatory lesions of the pituitary gland have been described. Lymphocytic hypophysitis is pathologically characterized by the diffuse infiltration of the pituitary gland by lymphocytes with the formation of lymphoid follicles and plasma cells, commonly seen in females during pregnancy or in the puerperium (8). Granulomatous hypophysitis, the other form of the inflammatory lesion of the pituitary gland, which is characterized by the infiltration of the gland by multinucleated giant cells, histiocytes, plasma cells, and lymphocytes, represents approximately 1% of sellar pathology approached via the transsphenoidal route (6). Granulomatous hypophysitis is seen in systemic granulomatous diseases; however, the cause is unclear in many instances (1–6). The inflammation generally affects the anterior lobe of the pituitary gland. Middle-aged and elderly women are reported to be affected predominantly (9). Granulomatous lesions of the pituitary gland can be an incidental autopsy finding and remain silent during life (6).
In the present case, a hypofunction of the pituitary gland was noted at the onset of symptoms. The patient later presented with ptosis and abduction deficit OD. Clinical and radiological diagnosis was pituitary adenoma; however, the biopsy was consistent with granulomatous hypophysitis. Hypophysectomy was not performed, and the symptoms regressed by the increased dose of steroid therapy given during the perisurgical period. After a 3-month asymptomatic period, the patient developed signs of right optic neuropathy. Bilateral optic nerve enhancement was detected in MRI, and the second eye became symptomatic during the hospital course. After the exclusion of possible causative systemic disorders such as tuberculosis, syphilis, or sarcoidosis, the patient was diagnosed with idiopathic granulomatous hypophysitis and treated with steroid therapy with excellent response.

In conclusion, this report documents a case of idiopathic granulomatous hypophysitis presenting with the symptoms of optic neuritis. To our knowledge, no other case of optic neuritis associated with this entity has been documented. In cases of optic neuritis, proceeding with the symptoms of hypopituitarism and ophthalmoplegia, the clinician should consider the possibility of parasellar pathologies, including a granulomatous lesion of that region. We recommend immunosuppressive treatment with corticosteroids after confirmatory biopsy and avoiding unnecessary surgical resection of the pituitary gland.

REFERENCES
Increased Endothelin-1 Plasma Levels in Patients With Multiple Sclerosis

Timo Haufschild, MD, Sidney G. Shaw, PhD, Jürg Kesseling, MD, and Josef Flammer, MD

Objective: We tested the hypothesis that the plasma level of endothelin-1 (ET-1) is increased in patients with multiple sclerosis (MS). The peptide ET-1 is one of the most potent known vasoconstrictors. An increased level of endothelin could explain some of the vascular symptoms of these patients.

Materials and Methods: A specific radioimmunoassay was used to determine ET-1 plasma levels. Twenty patients with MS were compared to 20 age- and sex-pair-matched healthy subjects.

Results: The plasma ET-1 levels were, on average, 224% higher in the patients with MS than in the controls (p < 0.005). The mean ET-1 levels (mean ± standard deviation [SD]) were 3.5 ± 0.83 pg/mL (min 2.13, max 5.37 pg/mL) in patients with MS and 1.56 ± 0.3 pg/mL (min 0.9, max 2.13 pg/mL) in healthy volunteers. Neither the different forms nor stages of MS had an influence on the results. The ET-1 level was also not correlated with the duration of the disease.

Conclusions: The plasma ET-1 level is markedly and significantly increased in patients with MS. Neither the cause of such an increase nor the pathogenetic role is known.

Key Words: Multiple sclerosis—Endothelin-1—Vascular dysregulation.

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system in which autoimmune mechanisms are relevant. In some patients with MS, signs of a vascular dysregulation can be observed (e.g., patients with MS show symptoms such as a tendency to cold extremities and migraine more often than healthy people) (1,2). This observation would be compatible with an increase of plasma ET-1. Furthermore, the possible involvement of vascular factors in the pathogenesis of the brain lesions or the symptoms has been discussed with controversy for decades (3,4).

The peptide endothelin-1 (ET-1), produced and released mostly but not exclusively by endothelial cells, is one of the most potent known physiologic vasoconstrictors. Because an increased plasma level of ET-1 could explain some of the vascular symptoms of patients with MS and because increased levels of endothelin were described in the cerebrospinal fluid of patients with MS (5), we tested the hypothesis that patients with MS have increased ET-1 plasma levels.

METHODS

The ET-1 plasma levels of patients with clinically defined MS (6)(10 males, mean age 43.8 ± 14.7 years, range 21–68 years and 10 females, mean age 41.6 ± 11.5 years, range 23–56 years) have been compared with the levels of healthy volunteers (10 males, mean age 45 ± 14.1 years, range 27–69 years and 10 females, mean age 41.7 ± 11.1 years, range 23–55 years). All patients with systemic conditions known to be associated with increased ET-1 levels were excluded from the study (7). At the moment blood was taken, all patients were mobile and in a stable phase of their disease. None had experienced a clinical relapse for at least 3 months. No patient was on any systematic medication. Written informed consent was obtained from all patients. Blood samples were taken after 30 minutes of rest in a supine position at room temperature. ET-1 plasma levels were determined by specific radioimmunoassay, as previously described (8). All values are expressed as mean ± standard deviation (SD). The ET-1 level of patients with MS was compared to age- and sex-pair-matched healthy subjects with the help of a dependent t-test. The influence of stages and types of MS were tested with an analysis of variance. The correlation with age and duration of MS was done with a Pearson correlation. A p value less than 0.05 was considered to be significant.

RESULTS

Plasma ET-1 levels were markedly and significantly elevated, by 224%, in patients with MS (p < 0.005) and averaged 3.5 ± 0.83 pg/mL (min 2.13, max 5.37 pg/mL) compared to 1.56 ± 0.3 pg/mL (min 0.9, max 2.13 pg/mL) in age- and sex-matched healthy volunteers (Fig. 1).

DISCUSSION

Our study shows that patients with MS have markedly increased ET-1 plasma levels. No correlation to age...
FIG. 1. Mean (± standard error of mean) plasma concentration of endothelin-1 (ET-1) in healthy controls and patients with multiple sclerosis (MS) (*p < 0.001).

could be found in healthy subjects or patients with MS. The different forms of MS and the different stages had no significant influence on the results. No correlation to the duration of the disease or to the mean Kurtzke Expanded Disability Status Scale (EDSS) could be found. An increased ET-1 plasma level in patients with MS goes with the finding of increased endothelin levels in the cerebrospinal fluid of patients with MS (5). Whether the increased ET-1 levels in patients with MS reflect an increased ET-1 production, a decreased metabolism, or a decreased excretion is not yet clear. An increase in ET-1 plasma level is not specific for MS. Similar plasma levels have been reported in patients with other autoimmune diseases, such as antiphospholipid syndrome, rheumatoid arthritis, and lupus erythematosus, and also in some infectious diseases, such as AIDS (7). Although increased endothelin levels were also found in the cerebrospinal fluid of patients with MS, the possible role of endothelin for neural transmission and regulation is not known and needs to be further investigated. In diabetic neuropathy, increased ET-1 activity exacerbates neural degeneration (reduction of nerve conduction velocity and endoneural blood flow) (9). In the case that ET-1 plays a role in the pathogenesis of MS, endothelin receptor blockers may offer some additional options.

Acknowledgments: The authors thank J. Boden, M. Joos, S. Lengen, and A. Zosso for expert technical assistance. This work was supported by the Swiss National Science Foundation (grant 32-49648.96).

REFERENCES
Comparison of Clinical Associations of Patients With Vasculopathic and Idiopathic Downbeat Nystagmus

Jeffrey L. Olson, MD, and Daniel M. Jacobson, MD

Objectives: To perform a pilot study comparing age and vascular risk factors of patients with vasculopathic and idiopathic downbeat nystagmus (DBN).

Materials and Methods: We reviewed the case records of 57 patients with DBN evaluated between 1987 and 1999, and classified each patient into three groups: vasculopathic, idiopathic, and other known causes. We then compared age and five weighted established stroke risk factors in patients with vasculopathic and idiopathic DBN.

Results: Of ten idiopathic cases, there were seven women and three men, ranging in age from 31 to 90 years (median, 79 years). Of the nine vasculopathic cases, there were seven women and two men, ranging in age from 50 to 86 years (median, 80 years). Using the Mann-Whitney U test, there was no significant difference between the two groups in terms of age (p = 0.84) or vascular risk-factor profile (p = 0.24).

Conclusions: The lack of significant difference between the two groups for age and vascular risk factors supports the hypothesis that some idiopathic cases of DBN may be caused by strategically located and radiographically occult cerebral infarctions.

Key Words: Downbeat nystagmus—Vascular risk factors—Stroke.

In published case series (1-4) of downbeat nystagmus (DBN), the most common causes were cranio-cervical structural disorders, cerebellar degenerations, toxic and metabolic disorders, multiple sclerosis, and strokes. Despite the many known causes of DBN, the etiology remains undetermined in 5 to 44% of patients (1-4). Our untested impression has been that many patients with idiopathic DBN are elderly with vascular disease. We postulated, therefore, that some cases of idiopathic DBN might be caused by occult strokes affecting the brainstem. To test this hypothesis, we performed the following exploratory pilot study to compare age and vascular risk factors in patients with vasculopathic and idiopathic DBN. A similar clinical profile, if found, in these two groups might support a possible cerebrovascular etiology for patients who have no overt cause identified after initial investigation.

METHODS

We reviewed the case records of all patients with DBN evaluated by one of us (DMJ) at a single institution between 1987 and 1999, and classified each patient into one of three groups: vasculopathic, idiopathic, and other known causes. We defined as vasculopathic those patients whose DBN was associated with other clinical signs, and radiographically verified changes, of cerebral infarction affecting the posterior fossa. After reviewing the literature, we compiled a list of other reported causes of DBN (Table 1). We classified cases as other known causes if the patient had any of these associations. Finally, we defined as idiopathic those patients whose symptoms were recently acquired, who had no prior documentation in the medical record of DBN, and who had no known cause.

We then compared age and five established stroke risk factors in patients with vasculopathic and idiopathic DBN. These risk factors—which included hypertension, coronary artery disease, atrial fibrillation, diabetes mellitus, and cigarette smoking—were weighted using published relative risk data (5) (Table 2). For each patient, we added the relative risk factor, if present, to derive a total vascular risk factor score. We then used the Mann-Whitney U test to compare the age and the derived composite vascular risk profile of the two groups. Although this study was retrospective, all patients were routinely queried about the presence of tobacco use and their general medical health, so that these variables were universally present in the medical records and available for abstraction.

RESULTS

Of the 57 patients with DBN evaluated during the study period, ten (18%) patients were classified as
TABLE 1. Reported causes and associations of downbeat nystagmus

| Cranio-cervical structural disorders          | Arnold-Chiari malformation                  |
| Basilar invagination                          | Paget disease                               |
| Syringobulbia                                 | Dolichoectasia of the vertebrobasilar arterial system |
| Tumors compressing the caudal brainstem      | Brainstem/cerebellar disease                |
| Cerebellar degeneration                       | Familial periodic ataxia                    |
| Posterior fossa strokes                       | Posterior fossa tumors                      |
| Paraneoplastic syndromes                     | Hydrocephalus                               |
| Hydrocephalus                                 | Frontoparietal                              |
| Trauma                                        | Multiple sclerosis                          |
| Tumors compressing the brainstem              | Toxic/metabolic disorders                   |
| Cerebellar degeneration                       | Chronic ethanol exposure                    |
| Posterior fossa strokes                       | Wernicke encephalopathy (vitamin B₁₂ deficiency) |
| Arnold-Chiari malformation                    | Vitamin B₁₂ deficiency                      |
| Basilar invagination                          | Magnesium deficiency                        |
| Paget disease                                 | Lithium                                    |
| Syringobulbia                                 | Phenytoin                                   |
| Dolichoectasia of the vertebrobasilar arterial system | Carbamazepine                              |
| Tumors compressing the caudal brainstem      | Felbamate                                   |
| Brainstem/cerebellar disease                  | Morphine–barbiturate combination            |
| Cerebellar degeneration                       | Toluene                                     |
| Familial periodic ataxia                     | Amiodarone                                  |
| Posterior fossa strokes                       | Other                                       |
| Paraneoplastic syndromes                     | Congenital                                  |
| Hydrocephalus                                 | Transient in the newborn                    |
| Hydrocephalus                                 | Familial, isolated                          |

idiopathic. There were seven women and three men, ranging in age from 31 to 90 years (median, 79 years). Downbeat nystagmus was neurologically isolated in all patients. As part of their work-up evaluation, all idiopathic patients underwent magnetic resonance imaging with special attention to the cranio-cervical junction. Diffusion or perfusion-weighted imaging was not performed. In addition, nine patients underwent magnesium determination and five patients underwent B₁₂ level determination. None of those patients were exposed to toxins or medications known to be associated with DBN.

Nine of 57 (16%) patients were classified as vasculopathic. There were seven women and two men, ranging in age from 50 to 86 years (median, 80 years). Using the Mann–Whitney U test, there was no significant difference between the two groups in terms of age (p = 0.84) (Fig. 1) or vascular risk-factor profile (p = 0.24) (Fig. 2).

DISCUSSION

Despite the various associations of DBN reported in the literature, the cause remains undetermined in a substantial proportion of cases. We were unable to assign a specific cause of DBN in 18% of the patients in our series. This frequency is consistent with the incidence of idiopathic cases identified in other large series of patients with DBN (1-4). It is possible, however, that some cases classified as idiopathic might have shown small infarcts (i.e., lacunar) if diffusion or perfusion-weighted magnetic resonance imaging was performed. It seems unlikely that this factor contributed substantially, if at all, to the misclassification of idiopathic patients, because none of them had other signs of posterior fossa injury.

In our pilot study, we found that idiopathic patients were generally elderly and possessed a similar vascular risk profile as those patients who have suffered posterior fossa strokes that caused DBN. The previously reported large series of patients with DBN did not provide information regarding vascular risk factors or age specifically in idiopathic cases (1-4).

![Figure 1: Comparison of ages of 10 patients with idiopathic downbeat nystagmus and nine patients with vasculopathic (indicated by infarction) downbeat nystagmus. The median ages of 79 years in the idiopathic group and 80 years in the vasculopathic group are represented by the horizontal bar in each column and are not significantly different (p = 0.84).]

![Figure 2: Comparison of the weighted vascular risk profile in the 10 patients with idiopathic downbeat nystagmus and nine patients with vasculopathic (indicated by infarction) downbeat nystagmus. The median values, represented by the horizontal bar in each column, are not significantly different (p = 0.24).]

**TABLE 2. Stroke risk factor relative risk**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>4.0</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>2.2</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2.9</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.7</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>1.7</td>
</tr>
</tbody>
</table>

Data adapted from Gorelick et al. (5).
The lack of statistical difference between the two groups for age and vascular risk factors supports the hypothesis that some idiopathic cases of DBN may be caused by strategically located and radiographically occult cerebral infarctions affecting the brainstem. Of course, our results should be tempered by the fact that the number of cases in the two groups was small, decreasing the overall power of our conclusions. On the other hand, despite the limitations imposed by a retrospective chart review, the variables we were interested in abstracting were universally present in all medical records of our patients, because each patient was specifically queried about the presence of these variables at the time they were initially evaluated.

In summary, our pilot study suggests that the similar age and vascular risk profile of patients with idiopathic and vasculopathic DBN implicates a common mechanism of injury that might explain the cause of DBN in some patients whose work-up evaluation proves unrevealing. We suggest a larger, and preferably prospective, study be performed to further test this hypothesis. A case-control design to compare vascular risk factors in each group with an unaffected population would enhance the validity of the conclusions. The use of pooled data from several sources would facilitate obtaining this data in a timelier manner.

REFERENCES
Pattern Visual Evoked Potentials in Malingering

Ayae Nakamura, MD, Tabuchi Akio, MD, Eiko Matsuda, and Yamaguchi Wakami

**Objectives:** We previously developed a new method for estimating objective visual acuity by means of pattern visual evoked potentials (PVEP). In this study, this method was applied to the diagnosis of malingering.

**Materials and Methods:** Six patients ranging in age from 40 to 54 years (mean 47 years) with suspected malingering were evaluated by means of the visual evoked potential test, optokinetic nystagmus (OKN) inhibition test, and the visual field test. In the PVEP study, the stimulus consisted of black and white checkerboards (39', 26', 15', and 9') with a visual angle of 8°, contrast level of 15%, and a frequency of 0.7 Hz. One hundred PVEP responses were averaged per session.

**Results:** Routine ophthalmic examinations were normal in all patients. Five patients had a tubularly constricted visual field, and the remaining patient had a normal visual field. The objective visual acuities of the six patients estimated from PVEP were better than their subjective visual acuities estimated with Landolt rings.

**Conclusions:** Among a variety of psychophysical and electrophysiologic ancillary tests, we consider our PVEP method a useful method for objectively determining visual acuity in a patient with signs of ocular malingering.

**Key Words:** Ocular malingering—Pattern visual evoked potentials (PVEP)—Visual acuity.

**PATIENTS AND METHODS**

**Patients**

Six patients ranging in age from 40 to 54 years (mean 47 years) had clinical signs of ocular malingering. They were referred from other ophthalmologists or courts of law. Fifteen eyes of 14 age-matched healthy adults were used as controls (mean 46 years). Examinations of patients and subjects included visual acuities with Landolt rings, tests of papillary reaction to light, visual fields tests looking for signs of tubular constriction, ophthalmoscopic examination, OKN inhibition tests, and our PVEP recordings. PVEPs were always performed with appropriate refractive correction. This investigation was performed according to the guidelines of the Helsinki Declaration after informed consent was obtained from all subjects.

**Stimuli**

For PVEP recording, each subject viewed a white and black checkerboard pattern on a television monitor. The checkerboard stimulus subtended a visual angle of 8°, and the contrast was 15%. The check sizes were 39', 26', 15', and 9'. The checks were reversed at 0.7 Hz. The computer analysis time of the PVEP was 512 milliseconds, measured by a Signal Processor DP1200 (NEC Sanei, Tokyo, Japan).

**Recording methods**

One experimenter monitored the patients' ocular fixation, which was directed toward the TV screen in a shielded room as a monocular PVEP was recorded. Recording scalp electrodes were placed on 16 sites according to the international 10 to 20 method. The reference electrodes were attached at A1 and A2, and the forehead was grounded. Signals were amplified with a preamplifier. The bandpass was 1.59 to 70 Hz, and the artifact reject was 100 μV peak-to-peak.

**DATA ANALYSIS**

The P100 component of Oz was used to estimate objective visual acuity. The PVEP recorded from healthy adults showed a close correlation between the relative...
amplitude of the PVEP to different check sizes and subjective visual acuity (20). Visual acuity of 0.1 corresponded to the 39' pattern, 0.2 to the 26' pattern, 0.5 to the 15' pattern, and 1.0 to the 9' pattern. Responses to the 39' pattern but not to the 26' pattern were considered nearly equivalent to a visual acuity of 0.1. Statistics for the patients and controls were evaluated by the unpaired t-test.

RESULTS

The clinical characteristics of our patients, including sex, age, visual acuity with Landolt rings, PVEP visual acuity, and visual fields, are summarized in Table 1. Four patients had histories of trauma in traffic accidents (patients 1, 2, 3, and 5). Two patients had documented abnormalities in the fellow eye (patients 4 and 6). Patient 4 had optic atrophy in the fellow eye resulting from head trauma, and patient 6 had retinal detachment in the fellow eye resulting from ocular trauma. Tubularly constricted visual fields were found in patients 1, 2, 3, 5, and 6, whereas patient 4 had a normal visual field. Ophthalmic examination results, including pupillary light reactions, were normal. Computed topographic scanning results of the brain and orbits were normal in patients 1, 2, 3, 5, and 6. The OKN inhibition test was performed on two patients. In patient 2, visual acuity with the OKN inhibition test was 1.5 OD, whereas in patient 6, visual acuity with this test was 0.5 OS.

The PVEP visual acuities of all the patients were better than their subjective visual acuities with optical correction. The latencies of the P100 components tended to be shorter in the patients than in the controls (Table 2), but the unpaired t-test showed that the difference in the latencies of the P100 component between the patients and controls was significant with only the 9' pattern ($p < 0.05$). The patients' P100-component amplitudes were nearly equal to those of the controls' and were not statistically significant (Table 3).

Figure 1 shows a control's PVEP OD. She was a 47-year-old Japanese woman. Because the P100 component of O1, O2, and Oz were recorded, the PVEP visual acuity OD was judged to be 1.0. The P100 components of Oz were obtained from 13 of 15 eyes in the controls. The accuracy for visual acuity of the controls was 86.7% for 0.1, 0.2, 0.5, and 1.0.

Patient 1 was referred to our hospital in February 1995 because of unaccountable visual loss after a truck collision in September 1993. On ophthalmic examination, corrected visual acuity was 0.3 OD and 0.4 OS. Critical flicker frequency (CFF) OD was 32, 31, and 36 Hz, and those values OS were 25, 31, and 34 Hz. He had normal pupillary reflexes, normal anterior segments, normal ocular media, and normal fundi. The visual fields OU were tubularly constricted.

Figure 2 shows the patient's PVEP. In the PVEP with the 39' pattern, there were P100 components of O1, O2, and Oz. With the 26' pattern, there were also P100 components of O1, O2, and Oz. With the 15' and 9' patterns,
Objective assessment of visual acuity was performed on patients with clinical signs of ocular malingering using PVEP. Tyler et al. (15,16) and Nelson et al. (17,18) were using the sweep technique to determine visual acuity. In this study, the PVEP was recorded with low-contrast stimulation with a small angle and low frequency, and the transient technique was also used. Generally, stimulation has been set with high contrast in the PVEP (6-8,12,13), but high contrast activates motion perception (21,22), whereas low contrast tends to activate form sensation. Accordingly, we decided to use a low-contrast rate of 15% in this study.

Regan (23) reported that 5 to 9 cycles per second evoked the greatest responses for small patterns of about 10°, whereas larger patterns of 40° resulted in the greatest responses at temporal frequencies of 10 to 20 cycles per second. In this study, the 9° pattern was used to measure visual acuity of 1.0 using the PVEP. The frequency of 0.7 Hz was then determined.

First, we investigated the PVEP with low contrast and low frequency. De Keyser (14) reported that there was a linear relation between log subjective visual acuity and log check size of the PVEP. In reference to that finding, the check sizes of the patterns used were 39', 20', 13', and 9'. However, the 20' and 13' patterns with a visual acuity of 0.2, and the 13' and 9' patterns with a visual acuity of 0.5 elicited the P100 components. Visual acuities of 0.2 and 0.5 could not be determined by this method. Having met with failure in our first study, we revised our method to deal with a number of its problems.

One problem was considered to be the angle of the 35 x 26-cm television screen that was used. Because the retinal X-ganglion cells are suggested to be the ones predominantly stimulated (19,20,24), the angle of the stimulus needed to be smaller. Therefore, the visual angle of 8° was chosen for this study. A second problem was that the graphic correlation differed between the 20' and 13' patterns and the visual acuity of 0.2 and 0.5. Therefore, the checkerboard stimuli were changed from 20' and 13' patterns to 26' and 15' patterns. When the PVEP was recorded with these stimuli, the accuracy for visual acuity was 76.9% for 0.1, 71.4% for 0.2, 70.0% for 0.5, and 58.3% for 1.0 in 18 healthy eyes (mean 22 years) (19). This result was not enough to measure visual acuity of 1.0. Therefore, in this study, PVEP of controls in the fifth decade was initially recorded using the procedure described above. The accuracy for visual acuity of 1.0 was 85.6%. Thus, this method was thought to be applicable to estimation of visual acuity.

There are two problems in measuring PVEP with this method. One problem is fixation. If the patient cannot stably fixate, PVEP visual acuity cannot be assessed. In this study, visual acuity could be measured in six patients with good fixation, but another patient with suspected malingering could not be assessed using the PVEP. He complained of left ptosis and visual loss after left ocular trauma. When it was stressed that he should open his left eye, his eyes deviated in a right downward direction. Then the PVEP could not be performed with this patient.

A second problem is that this method is time consuming. It requires 1 hour to measure the visual acuity OU. Therefore, this method needs to be improved to shorten the examination time.

DISCUSSION

The same findings were noted. PVEP visual acuity was 1.0 OU.

FIG. 1. Pattern visual evoked potentials records for the 39', 26', 15', and 9' patterns from one healthy adult. The P100 components were always present.

FIG. 2. Pattern visual evoked potentials records for the 39', 26', 15', and 9' patterns from one patient with suspected malingering. The P100 components were always present.
CONCLUSION

We evaluated objective visual acuity using the PVEP in patients with ocular malingering. PVEP can be useful in objectively establishing the true acuity in an eye that a patient is spuriously claiming to be impaired.

Acknowledgment: The authors thank William F. Hoyt, MD, of the University of California, San Francisco, for his critical reading of the manuscript. This study was presented in part at the 12th International Neuro-Ophthalmology Symposium, Dublin, Ireland, July 19–22, 1998.

REFERENCES

Systemic Disease and Neuro-ophthalmology: Annual Update 2000 (Part I)

Anthony C. Arnold, MD, and Andrew G. Lee, MD

In part I of this annual update, we review current aspects of multiple sclerosis and stroke therapy and the paraneoplastic syndromes of the retina and optic nerve.

THERAPY OF MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a common demyelinating disease of the central nervous system (1–86), with substantial long-term neurologic consequences (1,4,9,25,34,52,54,55,57,60,63,65). After 10 years with MS, 50% of patients are unable to perform household and occupational responsibilities; after 15 to 20 years, 50% are unable to walk without assistance; after 25 years, 50% are unable to ambulate. The average annual cost of MS in the United States is greater than 6.8 billion dollars (1). There are three main subtypes of the disease: relapsing remitting (RR), secondary progressive (SP), and primary progressive (PP).

This update reviews the current status of MS therapy (1–86). We have chosen to focus on the new and emerging immunomodulatory therapies for disease relapses and the treatments to prevent disease progression. We do not review the treatments for common MS-related sensory and motor symptoms, fatigue, or depression (35).

Corticosteroids

Corticosteroids such as prednisone, dexamethasone, and methylprednisolone (MP) have been the mainstays of therapy for acute exacerbation in MS (1,4,9,25,34,52,54,55,57,60,63,65,67). The mechanisms of action include reduction in CD 4 cells, decreased cytokine release, and decreased class II expression. Although there have been few studies demonstrating advantages of one type of steroid rather than another, intravenous MP has emerged as the most frequently used acute short-term (3–5 days) therapy for exacerbations.

Some authors have proposed the use of high-dose (e.g., 500 mg) oral MP (9), and there may be a role for oral therapy in selected cases. Survey information has shown wide variability in the dose, route of administration, duration, venue, and indication for steroid use in MS among treating neurologists (76). The issues surrounding oral versus intravenous steroids remain controversial. Both prednisone and MP are well absorbed orally, and oral therapy is less expensive than intravenous therapy. Some clinicians use low-dose oral prednisone for minor exacerbations and reserve intravenous therapy for major relapses (70). Although some authors have used intravenous pulse MP for progressive disease, there is only limited evidence that steroid treatment impacts the long-term course of MS (51).

High oral doses theoretically increase the risk for gastric ulceration. Metz et al. (24) studied 17 patients treated with 1250 mg of oral prednisone per dose and 1000 mg of intravenous MP. Three (25%) patients in the oral group and two (40%) patients in the intravenous group had modestly abnormal gastric permeability (95% CI 34–64%, p = 0.6). These authors concluded that short-term high-dose oral prednisone was not associated with greater gastric damage when compared to intravenous MP.

Corticosteroids in optic neuritis. The Optic Neuritis Treatment Trial (ONTT) previously established that intravenous MP in typical optic neuritis improved the speed of visual recovery but did not impact final visual outcome. Oral steroids in conventional doses increased the rate of new attacks and were discouraged by the ONTT. Wakakura et al. (84) reported a randomized controlled clinical trial comparing intravenous MP with a control drug (mecobalamin) for managing optic neuritis. The intravenous MP group showed faster recovery of vision, but the visual function at 12 weeks and 1 year were essentially the same in the two treatment groups.

Sellebjerg et al. (85) assessed the efficacy of oral high-dose MP in acute optic neuritis. These authors concluded that oral high-dose MP improved speed of recovery, but there was no difference in outcome at 8 weeks or on subsequent attack frequency.

Trobe et al. (86) performed a survey to determine whether the ONTT results altered the practice patterns of...
ophthalmologists and neurologists. In accordance with the ONTIT, nearly all surveyed ophthalmologists and neurologists had reduced their use of oral prednisone alone, and most of these professionals used intravenous MP. Many clinicians, however, mistakenly believed that intravenous MP improved final visual outcome. Only 7% of neurologists and 36% of ophthalmologists (p = 0.0001) in this survey were adhering to the ONTT suggestion to use MRI findings as a basis for treatment.

**Immunomodulatory agents**

- **Interferons.** Four classes of interferon (IFN α, β, γ, and ω) are recognized. Initial studies of IFN γ showed an increase in relapse rate in MS, despite the fact that it reduced experimental allergic encephalitis in mice. IFN γ is not currently used in MS therapy. IFN α and β are type I IFN and have many effects that counter IFN γ. IFN-α trials, however, have provided mixed results. In some studies, IFN α-2a reduced exacerbation rate and magnetic resonance (MR) activity in MS (13). Myhr et al. (66), however, in a randomized placebo-controlled trial of IFN α-2a (n = 97), reported reduced MR lesions but no treatment effect on exacerbation rate, progression of disability, or quality of life (QoL). The value of IFN α in clinical use is uncertain. IFN β is an immunomodulatory agent that affects T-cell function and has an established beneficial role in MS (2,5-7,9-16,27-29,30,32-33,36,41,44-46,49,50,56,58-59,70-73,75,78-83). Interferon β-1b (Betaseron; Berlex Laboratories, Richmond, CA) is a nonglycosylated E. coli recombinant product. It differs from IFN β-1a by one amino acid and is administered subcutaneously. IFN β-1a (Avonex [Biogen, Cambridge, MA]) is a glycosylated protein derived from Chinese hamster ovary cells. It is identical to human IFN and is injected intramuscularly once weekly (1,4,9,25,34,52,54,55,57,60,63,65).

  - **Mechanism of action of interferons.** The mechanisms of action for IFN effect in MS are largely unknown. IFN have been documented to inhibit migration of T cells, enhance major histocompatibility complex (MHC) class I and inhibit MHC class II expression on monocytes, have antiviral effects (2,5-7,9-16,27-29,30,32-33,36,41,44-46,49,50,56,58-59,70-73,75,78-83). Interferon β-1b (Betaseron; Berlex Laboratories, Richmond, CA) is a nonglycosylated E. coli recombinant product. It differs from IFN β-1a by one amino acid and is administered subcutaneously. IFN β-1a (Avonex [Biogen, Cambridge, MA]) is a glycosylated protein derived from Chinese hamster ovary cells. It is identical to human IFN and is injected intramuscularly once weekly (1,4,9,25,34,52,54,55,57,60,63,65).

  - **Treatment results of interferons.** Interferon β-1b has multiple effects in RR MS, including reduction of relapse rate (33%), reduction of new MRI lesions, and reduction of MRI lesion volume. IFN β-1b may also reduce relapse rate, clinical disability progression, and MRI lesion volume in SP MS. IFN β-1a has been shown to reduce progression of disability, rate of relapse, new MRI lesions, and MRI lesion volume (2,5-7,9-16,27-29,30,32,33,36,41,44-46,49,50,56,58-59,70-73,75,78-83).

  - More recent studies have confirmed the benefit of IFN β therapy seen in previous clinical trials. Weekly IFN β-1a has been shown to decrease the rate of new enhancing lesions on MRI. Gasperini et al. (79) showed a stabilizing effect on T1-weighted hypointense lesion volume (n = 67) in RR MS. Miller et al. (27) performed a randomized placebo-controlled trial of IFN β-1b (n = 718) in SP MS with a follow-up period of up to 3 years. There was a 15% increase in MR lesions from baseline to last MR scan in the placebo group. In contrast, there was a significant reduction in MR lesions at year 1 (4%) and year 2 (5%) for the treatment group. Paolillo et al. (46) reported that the duration of MR enhancement and the number of new enhancing lesions were lessened by IFN β-1a treatment. The clinical significance of these changes in MR findings is still debated. There is increasing evidence that MR abnormalities are objective and quantifiable measures of treatment effect in MS. Rovaris (11,77), however, reviewed MRI findings and long-term disease evolution in MS in trials. They found only a variable clinical correlation ranging from poor to moderate.

  - Li and Paty (50) reported the results of the Prevention of Relapses and Disability by Interferon-beta-1a Subcutaneously in Multiple Sclerosis (PRISMS) trial. This study was a double-masked, randomized, multicenter.

MRI lesions (83). Waubant et al. (82) reported a reduced MRI findings of IFN (β-1a at low dose in MS. There was relatively less effective than higher and more frequent phase III, placebo-controlled study of IFN (β-1a

48 clinical effect, and significant opportunity cost. They treated for 30 months, six relapses would be prevented. The high-cost variables in their treatment was high. The high-cost variables in their study remained controversial and continued study is warranted.

Side effects of interferons. Adverse effects with IFN β are common and especially frequent during the first weeks of treatment. Flu-like symptoms occur in as many as 75% of patients. The side effects include fever, chills, myalgia, insomnia, anorexia, weight loss, fatigue, and injection-site reactions (7,10,22,28,59). The effects may be more frequent in women (10). Transient laboratory abnormalities, neuropsychiatric changes, menstrual disorders, and increased spasticity may also occur. Walth reviewed other possible side effects including various autoimmune reactions, capillary leak syndrome, anaphylactic shock, thrombotic-thrombocytopenic purpura, insulin, headache, alopecia, and depression (28). These side effects may result in reduced treatment compliance or discontinuation of therapy. Efforts to minimize these reactions include appropriate management of mild side effects with analgesics and antipyretics such as ibuprofen, acetaminophen, and pentoxyfylline. The use of correct preparation, careful injection technique, and modification of the dosage may be helpful. Bayas et al. (7) reviewed the management of these adverse effects. Ibuprofen and gradual introduction of the drug may reduce the incidence of flu-like symptoms to rates comparable with placebo.

Quality of life and interferon therapy. Patients with MS often have a normal lifespan, and, therefore, QoL parameters are important outcome measures. Rice et al. (33) reported that patients with RR MS (n = 117) treated with IFN β-1b had a better QoL than untreated patients. Nortvedt et al. (32) performed a randomized double-masked placebo-controlled treatment trial of 97 RR MS patients. These authors found a relationship between new enhancing MR lesions and reduced QoL among the placebo patients but not the IFN patients. Treatment with IFN α-2a does not seem to improve patient QoL after 6 months, despite marked effect measured by MRI. The Canadian Burden of Illness Study Group reported that the QoL of MS patients falls drastically and early in the disease. Treated patients with RR MS had better QoL than untreated historical controls. This finding was especially true for those patients with an Expanded Disability Status Scale (EDSS) less than 3.0. Continued work on QoL measures will be important for future treatment trials.

Neutralizing antibodies to interferons. Neutralizing antibodies (NAbs) to IFN develop in 8 to 40% of cases. The clinical significance of this finding is unclear but may be associated with reduced IFN efficacy (29). Antonelli et al. (29) examined the specificity of NAbs to IFN β-1a or IFN β-1b and studied the effect of switching from IFN β-1a to IFN β-1b. All positive sera independent of the source may recognize both forms of IFN β. They concluded that it was unlikely that administration of IFN β-1b to anti-IFN β-1a NAbs-positive patients could overcome any inhibitory effect exerted by the serum NAbs and vice versa.


Glatirimer acetate (Copaxone). Glatirimer acetate (Copaxone; Teva Pharmaceuticals USA, Kansas City, MO), formerly Copolymer I, is a synthetic polypeptide of four amino acids, including glutamic acid, lysine, alanine, and tyrosine. The chemical structure resembles myelin basic protein (1,4,9,25,34,52,54,55,57,60,63,65). Its mechanism of action is unknown but it has been shown to reduce the relapse rate in MS (29%). It has also been reported to slow disease progression. The effect of glatirimer acetate on the number and activity of lesions on MR is less clear than the beneficial effect seen for IFN. The drug is administered subcutaneously once per day (57,80).

Side effects of glatirimer acetate. The side effects of glatirimer acetate are mild and include injection-site reactions. There are idiosyncratic reactions in as many as 15% of patients and the self-limited symptoms include facial flushing, palpitations, and chest tightness (1,4,9,25,34,52,54,55,57,60,63,65). NABs to glatirimer acetate are of unknown clinical significance.

Comparing the three immunomodulatory agents (IFN β-1b, IFN β-1a, and glatirimer acetate). There are no data directly comparing the relative efficacy of these three drugs in a single study (1,4,9,25,34,52,54,55,57,60,63,65). Rudick (1) summarized the supporting evidence for the use of each agent. The arguments for IFN β-1b when compared to IFN β-1a include: 1) more beneficial MRI effect on T2-weighted lesion accrual after 2 years, 2) higher weekly dose, and 3) larger reduction in relapse rate. The arguments for IFN β-1a include: 1) reduced disability progression, 2) fewer injection-site reactions, 3) less theoretic immunogenicity, 4) improved patient convenience enhanced by weekly dose, and 5) more favorable side-effect profile. The arguments for glatirimer acetate are: 1) it is better tolerated than IFN β and 2) it circumvents the problem of NABs.

Prophylactic interferon therapy: Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study. Whereas treatment with IFN has been shown to benefit patients with established MS, its value for the prevention or reduction of later development of demyelinating lesions after a first clinical event has been proven. Initial results from the Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study (CHAMPS) suggest that treatment with IFN β-1a may reduce the risk of clinically definite multiple sclerosis (CDMS) after such an event (87). The study was a multicenter randomized, double-masked, placebo-controlled trial of 383 patients with an initial neurologic event consistent with demyelination, including 192 (50%) patients with optic neuritis and MR evidence of subclinical brain lesions (at least 2 typical MS lesions 3 mm in diameter). Subjects were treated with intravenous and oral corticosteroids within 14 days of the event and subsequently randomized to weekly intramuscular injections of either placebo or 30 μg of IFN β-1a within 27 days of the initial event. The trial was terminated at the interim analysis of efficacy after 3 years, when a beneficial effect was demonstrated. Data indicated that the cumulative probability of developing CDMS was 35% in the treated group versus 50% with placebo. The volume of new, enlarging, and enhancing MR lesions was significantly lower in the treated group. Treatment with IFN β-1a reduced, by approximately 50%, the rate of development of CDMS within 3 years after an initial event. The practical clinical implications of the study for therapy of patients with initially isolated optic neuritis have yet to be established.

Immunoglobulin therapy. Intravenous immunoglobulin (IVIg) therapy has been shown to variably reduce exacerbations and MR-enhancing lesions in MS. The mechanism is unknown but may be related to anti-idiotypic effects or TNF-β suppression (1,4,9,25,34,52,54,55,57,60,63,65). In several small nonrandomized studies, there was a reduced rate of disability and activity of disease on MRI. In animal models and in a few open trials, IVIg treatment enhanced central nervous system remyelination (8,61,65,73). Stangel et al. (8) conducted a double-masked placebo-controlled pilot study (n = 10) of IVIg at a dose of 0.4-gm/kg body weight for 5 consecutive days. There was no difference in the primary outcome of central motor conduction times after treatment. IVIg is associated with minor side effects including fever, malaise, headache, and rash. There are a few major side effects, including aseptic meningitis, renal failure, and thrombosis. The availability of alternative immunomodulatory agents such as IFN and glatirimer acetate therapy, the high cost of 1800 dollars per infusion for IVIg, and the recent decreased availability of IVIg in the United States have limited its use for MS (8,61,65,73).

Immunosuppressive therapy

Azathioprine, methotrexate, cyclosporine, and cyclophosphamide. Nonspecific immunosuppressive agents such as azathioprine (Imuran; Faro Pharmaceuticals, Bedminster, NJ), methotrexate (Rheumatrex; Novartis Pharmaceuticals, Pearl River, NY), cyclosporine, and cyclophosphamide (Cytoxan; Bristol-Myers Squibb, Princeton, NJ) have shown some limited efficacy in MS (1,4,9,19,24,25,34,40,52,54,55,57,60,63,65). Azathioprine works by cell-mediated and humoral immune mechanisms. In meta-analyses of randomized controlled trials, this drug reduced relapse rates by one third and reduced progression of disability in MS (80). Side effects, including hematologic and gastrointestinal effects, however, may outweigh its benefit. Methotrexate also works by cell-mediated and humoral immune mechanisms and has reduced progression of upper limb impairment, but not other measures, in one study (51,80). Cyclosporin A may also have a modest effect on MS progression but has significant nephrotoxicity (80). Further studies are needed to determine the potential role of these agents.

Several nonmasked nonrandomized trials have shown a potential benefit for cyclophosphamide in MS (19,40). Other studies, however, including one randomized, masked, placebo-controlled trial showed no improvement in SP MS (40). Hohol et al. (19) studied combined
pulse therapy with cyclophosphamide and MP at 4- to 8-week intervals in an open-label trial of 95 subjects with MS. They concluded that there was some benefit to treatment, especially for SP MS, that was refractory to immunosuppressive therapy, recommending that earlier intervention should be considered in these patients. Gobbi et al. (40) evaluated cyclophosphamide in five MS patients who failed an average of three previous other treatments. All patients showed a rapid reduction in MR contrast-enhancing lesion frequency (40).

**Mitoxantrone and mizoribine.** Mitoxantrone is an antineoplastic DNA-reactive agent that has demonstrated a significant reduction in relapse rate, delayed time to first relapse, and slowed progression of disease in SP MS (9). Unfortunately, significant side effects, including cardiac toxicity and neutropenia, may limit its use. Mizoribine (MZR) is an imidazole nucleotide that inhibits purine synthesis and helper T-cell function and is used in Japan as an immunosuppressant for chronic rheumatoid arthritis. MZR, in one multicenter, double-masked, placebo-controlled trial, showed no benefit in the primary endpoints of relapse rate and MR lesion area (47). Saida et al. reported 24 MS patients treated with MZR and corticosteroids in an open trial. The mean relapse rate per year at entry was decreased after 2 years (47).

**Other therapies**

**Sulfasalazine.** Sulfasalazine is an anti-inflammatory drug used in the treatment of various rheumatologic diseases. The Mayo Clinic–Canadian Sulfasalazine Study was a randomized, double-masked, placebo-controlled trial of 199 RR and SP MS patients (17). The trial reported that sulfasalazine temporarily reduced relapse and progression rates, delayed time to first relapse, increased the number of relapse-free patients, and decreased MR activity of MS. The effect was seen in the first 18 months of the trial but not thereafter. The authors concluded that the drug did not prevent EDSS progression.

**Roquinimex.** Roquinimex is a synthetic immunomodulatory agent that has been studied in three phase III trials, all showing marginal efficacy. Substantial adverse effects, including musculoskeletal pain and myocardial infarction, were noted (80).

**Cladribine (Leustatin).** Cladribine (Leustatin; Ortho Biotech, Inc., Raritan, NJ) is a specific antilymphocyte agent that may reduce disability, MR lesions, and CSF oligodendrocyte bands in MS (9,42,57,74,76). Romine et al. (74) conducted an 18-month, randomized, placebo-controlled, double-masked, phase II study of cladribine in 52 patients with RR MS. There was a statistically significant favorable effect on the frequency and severity of relapses and MRI disease activity. Cladribine is well tolerated but may cause lymphopenia and may potentiate herpes zoster virus (25%) or other opportunistic infections (74).

**Interleukin-1 receptor antagonist.** Transmigration of leukocytes across the blood–brain barrier into the CNS may play a role in demyelination and oligodendrocyte damage in MS. Lenkarrast is a white blood cell antibody that blocks transport across the blood–brain barrier. It showed no clinical effect in one trial (40).

**Plasma exchange.** Anecdotal reports of plasma exchange have suggested benefit for patients with MS, although the mechanism is unknown (26,31,43,62). Weinshenker et al. (26) conducted a randomized, sham-controlled, double-masked study of plasma exchange without concomitant immunosuppressive treatment for patients with recently acquired severe neurological deficits resulting from attacks of inflammatory demyelinating disease. All of these patients had failed to recover after treatment with intravenous corticosteroids. Moderate improvement in neurologic disability occurred in 8 of 19 (42.1%) courses of treatment, compared with 1 of 17 (5.9%) courses in sham treatment. The Canadian Apheresis Group reviewed their data on 103,416 plasma exchange procedures, including management of MS. In the meta-analysis, there was no apparent benefit if the studies were corrected for multiple comparisons, blinded observations, and exclusion of patients not adhering to standard entry criteria (43).

**Extracorporeal photopheresis.** Rostami et al. (48) performed a randomized, double-masked, placebo-controlled with sham therapy trial of monthly extracorporeal photopheresis therapy in progressive MS (n = 16). No serious side effects occurred, but the treatment did not alter the course of disease.

**Lenercept.** Tumor necrosis factor is a proinflammatory cytokine that has been implicated in MS because it is toxic to oligodendrocytes and worsens experimental allergic encephalitis (EAE). Lenercept is a recombinant TNF-receptor p55 immunoglobulin fusion protein (sTNFR-IgG p55) that has been shown to be protective in EAE. The Lenercept Multiple Sclerosis Study Group and The University of British Columbia MS/MRI Analysis Group performed a double-masked placebo-controlled phase II study (n = 168) of Lenercept, failing to show any benefit in MRI study measures. Interestingly, the number of treated patients experiencing exacerbations was significantly increased (p = 0.007) (39). Studies of anti-TNF-α antibody have also had a negative result. The reason for the increased exacerbation rates is not clear.

**T-cell vaccination.** Myelin basic protein (MBP)-reactive T cells may be pathogenic in MS and may be depleted by T-cell vaccination (TCV). Immunization with autoreactive inactivated T cells may elicit specific immunity to pathogenic T cells. This approach is under active study by Hermans et al. (12). TCV with myelin basic protein–reactive clones can induce T-cell immune response and a clonal depletion of MBP-reactive T cells. Five years after TCV, MBP-reactive T cells were seen in five of nine MS patients, and these clones had a different clonal origin from those isolated before vaccination.

**Oral myelin.** Oral tolerance to fed antigen may result in active immune suppression or anergy (9). Oral myelin was not successful in reducing relapse rate, and there was no MRI effect when compared with placebo. Future studies with recombinant myelin peptides, possibly in conjunction with IFN therapy, may be forthcoming (57,76).
Monoclonal antibody (e.g., humanized anti-alpha 4 beta 1 integrin). Humanized anti-alpha 4 beta 1 integrin, in a randomized double-masked study, was well tolerated. It reduced MR lesions in RR and SP MS. Other studies, however, of humanized anti-CD 11/CD 18 integrin monoclonal antibody failed to show a clinical or MRI benefit (38). Monoclonal anti-CD4 antibody failed to show positive results in a double-masked, placebo-controlled, MR-monitored phase II trial (80).

Bone marrow and stem cell transplant. Bone marrow and stem cell transplants are being explored as potential management options in MS. These therapies have been tried in only a few patients (20). The morbidity and mortality rate of the procedure is significant (0.5-2.5%), and the results to date have been inconclusive.

Alternative therapy. Newland (64) reviewed the use and effectiveness of alternative therapy in MS. The author reviewed massage, imagery, acupuncture, aromatherapy, herbalism, therapeutic touch, and nutritional therapy. Increasing use of these alternative treatments by patients with MS may warrant further study, but there is little controlled clinical data to support efficacy.

Use of multiple sclerosis therapies in pregnancy and children. Olek (9) summarized the use of the selected MS treatments in pregnancy by category. Category A drugs have not been shown to be harmful. Category B drugs show no harm in animal studies, but no human studies have been conducted. Category B drugs include glatiramer acetate. Animal data show harm to fetus in category C drugs, but no controlled human studies have been conducted. Category C drugs include corticosteroids and IFN. Category D drugs are known to cause fetal harm in pregnant women. Category D agents include azathioprine, cladribine, and cyclophosphamide. Category X drugs are contraindicated in pregnancy and include methotrexate.

Although there have been no randomized clinical trials on IFN in children, Adams (49) reported good long-term treatment results with IFN beta-1b of a 7-year-old male with RR MS. More data is needed before recommendations can be made for children.

Future therapeutic strategies. Noseworthy (76) summarized possible future therapeutic strategies for MS in a 1999 review: 1) antiviral drugs such as valacyclovir and acyclovir, 2) cytokine and anticytokine strategies including TNF and other inhibitors, 3) "immune deviation strategies" to enhance Th2 cell/lymphokine predominance (penicillinylithine and TGF beta 10, 4) matrix metalloproteinase inhibitors such as D-penicillamine and hydroxyamantadine, 5) trimolecular complex strategies such as anti-MHC monoclonal antibodies, MHC class II hyper-variable peptide vaccines, anti-T cell monoclonal antibodies, altered peptide ligands, T-cell vaccination, and adhesion molecules, 6) calcitriol B inhibitors, 7) oxygen radical scavengers, 8) autologous bone marrow transplantation, and 9) gene therapy and implantation oligodendroglial precursors. Scolding (21) provided an interesting discussion of the potential management for long-term repair and remyelination in MS.

THERAPY OF STROKE

Antithrombotic therapy

Acute ischemic strokes may occur with white clots, because of platelet fibrin, or red clots, because of erythrocyte-fibrin pathology. White clots tend to occur in areas of high blood flow and red clots in areas of low blood flow. Antiplaquelet therapy includes aspirin (ASA), dipireno-ramide, ticlopidine, and clopidogrel. These agents would thus be theoretically better for white clots including carotid plaque disease without significant stenosis. Anticoagulation agents include heparin, low-molecular-weight heparin, heparinoids, and Coumadin (DuPont Pharma, Wilmington, DE). These drugs would theoretically be better for red clots. The red clot disorders include venous occlusive disease, large artery disease, or cardioembolic thrombo-embolism (88). The guidelines for antithrombotic therapy in cerebrovascular disease were reviewed by Albers and Tijssen (89). In this section, we review the emerging therapies for stroke including antiplatelet agents, anticoagulation, thrombolysis, statins, and neuroprotective agents (88-137).

Antiplatelet agents

Several clinical trials have indicated that patients with atherothrombotic stroke or transient ischemia may benefit from antiplatelet treatment. First-line therapy, therefore, might include ASA, ASA plus dipireno-ramide, ticlopidine, or clopidogrel (88). Transient monocellular blindness ("amaurosis fugax") resulting from transient ischemia is one possible indication for antiplatelet therapy. The large studies of ASA and other antiplatelet agents were not designed to consider this subgroup of patients.

Aspirin. Aspirin inhibits platelet release, aggregation, and adhesion by blocking cyclo-oxygenase. prostaglandins, prostacyclins, and thromboxane A2. It is the best studied and least expensive of the antiplatelet agents, and many large interventional studies have shown that ASA given within 48 hours modestly reduces mortality after stroke or transient ischemic attack (90,91). The ideal dosage is controversial, with no consensus even among stroke experts; although many clinicians in the United States use a 325-mg per day dose of ASA, some patients may require a higher dosage for therapeutic effect.

Albers and Tijssen (89), in a meta-analysis of ten clinical trials, reported a 13% relative risk reduction (RRR) in stroke, heart attack, or vascular death independent of ASA dose. ASA use was associated with an increased risk of hemorrhage of as many as two intracranial hemorrhages and four extracranial hemorrhages per 1000 treated patients, but the risk was offset by reductions in short- and long-term death and disability rates. Kalra et al. (92) performed a prospective cohort study of 1457 patients, 650 (45%) of whom were using ASA at a median dose of 75 mg and a range 75 to 300 mg. ASA was associated with lower 4-week mortality of 14% versus 20% (p < 0.01), independent of age, gender, and other risk factors. Maslar and Einhaupl (93) also found that...
ASA was clearly effective in reducing early death or stroke recurrence within the first few weeks.

Aspirin can be safely combined with low-dose subcutaneous heparin for deep venous thrombosis prophylaxis (90). Its use should be delayed by at least 24 hours if thrombolysis therapy is employed.

Nonarteritic anterior ischemic optic neuropathy and aspirin. Kupersmith et al. (134), in a retrospective study, suggested that aspirin may reduce second eye involvement in nonarteritic anterior ischemic optic neuropathy (NAION). Beck et al. (135), however, showed little or no long-term benefit to aspirin in reducing the risk of NAION in the fellow eye. These authors recommended caution in interpreting the results, because neither of these studies was prospective or controlled. It remains controversial whether ASA should be routinely recommended after NAION alone. The role of antiplatelet regimens other than ASA in the prophylaxis of NAION is poorly defined.

Diprydramidine. Diprydramine (DP) is a phosphodiesterase inhibitor that decreases platelet function by increasing levels of cyclic adenosine monophosphate and guanosine monophosphate. Conflicting data exist regarding the efficacy of ASA alone versus ASA combined with DP. Sivenius et al. (94) reported the data on 6602 patients in The Second European Stroke Prevention Study (ESPS2). In this study, there were four treatment groups: 1) placebo, 2) 2 x 25 mg of ASA, 3) 2 x 200 mg of DP, and 4) combination of 50 mg of ASA and 400 mg of DP per day. ESPS2 showed a benefit from antiplatelet treatment compared with placebo and an additional benefit using ASA combined with DP rather than either agent alone. ESPS2 data suggest that antiplatelet therapy does not influence the severity of recurrent stroke using the Rankin scale but does lengthen the stroke-free interval.

Ticlopidine and clopidogrel. Ticlopidine is a thienopyridine inhibitor of platelet aggregation. The Ticlopidine Aspirin Stroke Study showed that it reduces the risk of stroke when combined with ASA or when compared to ASA alone (95), but it has a high rate of side effects, including diarrhea (20%) and rash (10%). Serious and potentially life-threatening complications, including neutropenia and thrombotic-thrombocytopenic purpura, may occur in as many as 1% of patients.

Clopidogrel is an analogue of ticlopidine with an additional carboxymethyl side group and fewer hematologic side effects. In the Clopidogrel versus Ticlopidine (PRINCE) trial versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial (96), it reduced the risk of stroke but was no more effective than ASA alone.

Glycoprotein platelet IIb/IIIa complex antagonists. The glycoprotein platelet IIb/IIIa complex is the binding site for adhesive proteins such as fibrinogen. These proteins activate platelet aggregation and adhesion to blood vessels. Abciximab (ReoPro; Eli Lilly and Co., Indianapolis, IN) is a fragment, of a chimeric human/mouse monoclonal antibody that acts as a platelet glycoprotein IIb/IIIa antagonist. The Abciximab in Ischemic Stroke

Investigators performed a randomized, double-masked, placebo-controlled, dose-escalation trial in 74 patients after ischemic stroke (97). There were no cases of major intracranial hemorrhage. Asymptomatic parenchymal hemorraghes were detected on CT scan in 4 of 54 (7%) patients on abciximab compared with 1 of 20 (5%) patients on placebo. Six additional abciximab patients had asymptomatic hemorrhagic lesions detected by unscheduled brain imaging during their follow-up period. Investigators concluded that abciximab was probably safe when administered up to 24 hours after stroke onset, and it might improve functional outcome.

Anticoagulant therapy

Heparin and heparin analogs. Heparin is a biologic substance derived from bovine lungs and porcine intestine, which can be separated into low- and high-molecular-weight fractions. Its anticoagulant effect relates to binding of antithrombin III, inactivating thrombin and other serum protease coagulation factors, antagonizing thromboplastin, and interfering with the reaction of thrombin with fibrinogen to form fibrin. It does not potentiate recanalization of occluded arteries, and it has no neuroprotective properties; to date, no short-term or long-term benefit of heparin in acute ischemic stroke has been established. Heparin may, however, be useful for the following disorders: 1) acute intracranial dural and venous thrombosis, 2) presumed cardiogenic emboli with high risk of intracranial embolism, and 3) acute thrombi or severe large artery stenosis. Heparin is not recommended for hemorrhagic stroke or in cases with uncontrolled hypertension or high risk of bleeding.

Heparinoids are heparin analogs that have anticoagulant effects. Low-molecular-weight heparins (LMWH), such as enoxaparin, dalteparin, nadroparin, and tinzaparin, have better bioavailability and pharmacokinetics than heparin, and they result in fewer hemorrhagic complications, presumably because of their reduced effect on platelet function and vascular permeability. Either low-dose unfractionated heparin (UFH) or LMWH has been recommended for acute ischemic stroke patients with immobilized or paralyzed limbs who are at high risk for venous thromboembolism (VTED). Lensing et al. (98) reported that anticoagulation in high-risk patients reduced the risk of deep venous thrombosis and pulmonary embolism, but there was an increased risk of intracranial bleeding within 14 days of treatment. The incidence of thromboembolic events was 20% in patients randomized to enoxaparin compared with 35% in the UFH-treated group. In the Thromboembolism Prevention in Cardiopulmonary Diseases with Enoxaparin (PRINCE) trial, once-daily enoxaparin was compared to three-times-daily UFH. The PRINCE trial found that enoxaparin was at least as effective as UFH in reducing the risk of thromboembolic events by 19%. In high-risk predefined subgroups with heart failure, enoxaparin was significantly more effective (99).

Warfarin. Warfarin (Coumadin), an oral anticoagulant, inhibits vitamin K, a requirement for synthesis of factors II, VII, IX, and X. After acute use of heparin in
Thromboembolic disease (TED), warfarin allows clot organization and adherence to the vessel wall. Several studies have documented its efficacy, at a target international normalized ratio (INR) of 2.5, in atrial fibrillation. It may also be beneficial in other high-risk cardiac embolic diseases, and this question is being studied in clinical trials. Patients with cardiac thrombi or arrhythmia, prothrombotic cardiac lesions such as prosthetic heart valves, or some hypercoagulable states, including the presence of lupus anticoagulant, may require indefinite warfarin therapy.

Oral anticoagulant treatment for prevention of recurrent stroke in atherothrombotic, noncardiogenic embolic stroke, however, has not been sufficiently proven and may lead to increased hemorrhagic complications (89).

Thrombolytic therapy

Intravenous thrombolysis. Tissue plasminogen activator. Since 1990, clinical trials of intravenous thrombolysis for ischemic stroke have involved more than 3000 patients (100). Tissue-type plasminogen activator (tPA) was approved by the Food and Drug Administration (FDA) in 1996 after a large randomized placebo-controlled study by the National Institute of Neurological Disorders and Stroke (NINDS). The NINDS study showed a significant improvement in 3-month and 12-month outcomes with tPA at a dose of 0.9 mg/kg within 3 hours of onset. Hacke et al. (101–103) and Lyden (104) have reviewed the data from the NINDS and the first and second European Cooperative Acute Stroke Studies (ECASS I and II). The European trials showed comparable results but did not reach statistical significance for their primary endpoints. Nevertheless, the risk/benefit profile of tPA therapy based on the results of these three trials suggested that treatment was beneficial for selected eligible patients if administered within the 3-hour time window. At the 6-hour time window, a combined analysis of the three studies shows the number of disabled or dead patients was reduced. Devuyst and Bogousslavsky (105) believed that the results of these three studies must be interpreted with caution, however, and concluded that ECASS II was an "equivocal" study. Specifically, it was negative for the primary end point but positive in the post hoc analysis of modified Rankin scale scores dichotomized for death or dependency. These authors summarized the reasons for the controversy: 1) possible selection bias, 2) use of an uncommon primary end point, and 3) problems of power significance.

Clark et al. (106), in the Thrombolytic Therapy in Acute Ischemic Stroke Study, assessed the efficacy and safety of intravenous rtPA in 142 patients with acute (0–6 hours) ischemic stroke in a phase II, placebo-controlled, double-masked randomized study. A higher percentage of rtPA patients (40%) had a four-point improvement on the National Institutes of Health Stroke Scale (NIHSS) at 24 hours compared with placebo (21%) (p = 0.02). This early effect was reversed by 30 days when comparing the placebo group (75%) with the rtPA group (60%) (p = 0.05). Treatment with rtPA significantly increased the risk of symptomatic intracerebral hemorrhage (ICH) at 10 days (11%) versus placebo (0.01). The mortality rate at 90 days was also increased (23%) versus placebo (7%) (p < 0.01).

Albers et al. (107) performed a prospective, monitored, postapproval, multicenter trial with 389 consecutive patients in the Standard Treatment with Alteplase to Reverse Stroke Study (STARS). The median time to treatment was 2 hours and 44 minutes. The median baseline NIHSS score was 13. Thirty-five percent of patients had very favorable outcomes on the modified Rankin score (0–1), and 43% were functionally independent on the same scale (0–2). Thirteen patients (3.5%) experienced symptomatic ICH, of which seven were fatal. Twenty-eight patients (8.2%) had an asymptomatic ICH. Protocol violations were reported for 127 patients (32.6%). The following were favorable predictors: 1) less severe baseline NIHSS score, 2) absence of effacement or hypodensity of greater than 33% of the middle cerebral artery (MCA) territory or a hyperdense MCA on CT scan, 3) age less than 85 years, and 4) lower mean arterial pressure at baseline.

Tanne et al. (108) reported on 30 patients more than 80 years old compared with counterparts less than 80 years old (n = 159) included in the tPA Stroke Survey. In logistic regression models, there were no differences in odds ratio for favorable or poor outcome except for a tendency for higher in-hospital mortality in elderly patients (odds ratio, 2.8; 95% CI, 0.81–9.62; p = 0.10).

Caplan (109) reviewed seven studies of 370 patients of intravenous thrombolysis with rtPA. One third of patients showed significant recanalization compared with 5% of 58 controls. MCA occlusions seemed to demonstrate the best response.

The major risk of rtPA is ICH. The reported incidence of ICH is somewhat variable, including 3.3% in STARS, 6.4% in NINDS, 9% in the OSF Stroke Network (110), and as much as 20% in other series (111). Katzan et al. (112) reported a historical prospective cohort study of 3948 patients with ischemic stroke. Seventy patients (1.8%) admitted with ischemic stroke received intravenous tPA. Of these patients, 11 (15.7%) had a symptomatic ICH, and six of these were fatal. Half of the cases had deviations from national treatment guidelines. The authors concluded that the community Cleveland area experience with tPA for acute ischemic stroke may differ from that reported in clinical trials.

Buchan et al. (113) emphasized the need to follow protocol. They reviewed 68 consecutive patients with acute ischemic stroke treated with intravenous tPA within 3 hours of symptom onset. Fifty-seven patients were treated according to the NINDS protocol, with a mean baseline NIHSS score of 15 ± 6. Of these 57 patients, 26 (38%) made a full recovery, and 39 (57%) made an independent recovery. Eleven patients violated protocol and had a lower probability of independence (p < 0.02) or full neurologic recovery (p < 0.02). These patients also had a higher probability of symptomatic hemorrhage (p < 0.05) or death (p < 0.01).
Intravenous thrombolysis is believed to be most effective clinically under the following conditions: 1) when the occluded arteries are intracranial and relatively small, 2) when the thrombus is acute, 3) when recanalization occurs, and 4) for emboli rather than in situ thrombi in atheromatous plaques. Trouillas et al. (114) reported an open trial of intravenous rtPA (alteplase) for smaller intracranial arterial events administered within 7 hours of symptom onset. Seven of nine patients with anterior choroidal artery (ACHa) territory infarct had a primary early recovery within 6 hours after rtPA. Recovery was complete in five of seven patients. The authors concluded that AChA-territory strokes responded well to intravenous rtPA and hypothesized that this finding resulted from the small size of the artery and the clot.

Streptokinase. The three important randomized trials of intravenous streptokinase are the Multicentre Acute Stroke Trial–Italy (MAST-I), the Multicentre Acute Stroke Trial–Europe (MAST-E), and Australian Stroke Trial (115). These three trials were stopped because of high rates of brain hemorrhage, and this agent is not generally recommended. Wardlaw et al. (116) reviewed the influence of baseline risk postthrombolysis outcome in the MAST-I. The risk with streptokinase was similar in “severe” and “mild” strokes.

Intra-arterial thrombolysis. Two trials of intra-arterial (IA) prourokinase confirm the benefits of treatment for highly selected patients with angiographically confirmed proximal MCA occlusion if instituted within 6 hours after the onset of symptoms. IA direct thrombolysis has theoretical advantages over intravenous therapy: 1) faster and higher rates of complete recanalization, 2) lower required dosage of thrombolytic agent, and 3) smaller risk of hemorrhage (117). Abou-Chelb and Furlan (118) reviewed several IA thrombolysis studies and believed that IA therapy was at least as effective as intravenous thrombolysis. They cautioned, however, that unresolved issues remain before such therapy can become a part of the standard of care. Caplan (109) reviewed 17 (n = 449 patients) nonrandomized studies of IA thrombolysis. The drugs used included urokinase, streptokinase, and urokinase tissue plasminogen activator. Of the 449 patients, 299 (66%) experienced effective recanalization. Mainstream and divisional MCA occlusions (62%) had the best response. Basilar artery occlusions had a 62% recanalization rate. Internal carotid artery (ICA) occlusions had less response (45%). Distal MCA occlusions did not respond as well as proximal MCA occlusions. Forty-two percent (n = 197) of patients had a “good” outcome overall, and 18.5% of patients had ICH.

Lewandowski et al. (119) reported a double-masked, randomized, placebo-controlled multicenter phase I pilot study of intravenous rTPA or intravenous placebo followed by immediate cerebral arteriography and local microcatheter IA rTPA (n = 35). Recanalization was better (p = 0.03) in the intravenous/IA group. This pilot study demonstrated that combined intravenous/IA treatment is feasible and provides better recanalization. There was no evidence, however, of improved clinical neurologic outcome. Ueda et al. (117) reviewed 66 patients treated with IA thrombolysis within 6 hours of symptom onset. Multiple regression analysis suggested that age, residual cerebral blood flow (CBF), neurological score at baseline and the following day, and recanalization grade correlated significantly with long-term outcome.

Thrombolysis and central retinal artery occlusion. Hattenbach et al. and Wirostko et al. (136,137) have reported anecdotal successful thrombolysis in central retinal artery occlusion (CRAO). In the absence of prospective controlled clinical data, however, the benefit of thrombolysis for intraocular thrombosis remains controversial.

Role of new neuroimaging modalities. Newer imaging modalities for stroke include combined diffusion-weighted and perfusion magnetic resonance (MR) scans, MR angiography, xenon CT and CT angiography, transcranial Doppler ultrasound, and positron-emission tomograph (PET) scans. These new modalities can provide important information about vascular occlusion, potential reversibility of ischemia, and brain function (121). Albers (120) emphasized the expanding role for early MR imaging in acute stroke, suggesting that such acute MR imaging may eventually prove superior to CT for identification of patients eligible for thrombolytic therapy. Tong and Albers (122) reviewed the utility, indications, and potential future role for diffusion/perfusion-weighted MR imaging, which may play a substantial role in determining the suitability of acute stroke patients for thrombolytic therapy. Early perfusion-weighted imaging (PWI) may show blood flow abnormalities and acute dysfunctional brain tissue. Acute diffusion-weighted imaging (DWI) lesion may correspond to the core of the early infarction. Mismatch between the acute PWI lesion and the smaller DWI lesion may represent potentially salvageable but poorly perfused brain tissue surrounding the infarct. In patients with PWI/DWI mismatch, early reperfusion may be associated with clinical improvement and reversal or reduction of DWI lesion growth.

Alexandrova et al. (123) reported the use of transcranial doppler (TCD) with low MHz frequency to determine arterial occlusion and continuously monitor recanalization in 40 patients treated with tPA. Clinical lack of improvement or worsening was associated with no recanalization, late recanalization, or reocclusion on TCD (p < 0.01). Recovery was associated with recanalization on TCD.

Central benzodiazepine receptor ligands, such as 11C flumazenil (FMZ), are markers of neuronal integrity and may be useful in the future for differentiation of functional and morphologic stroke damage. Heiss et al. (124) studied 11 patients with acute hemispheric ischemic stroke treated with alteplase using cortical cerebral blood flow, FMZ binding, and PET. Hypoperfusion was observed in all cases, and they concluded that FMZ PET may distinguish between irreversibly damaged and viable penumbra tissue early after acute stroke.
Other potential agents in stroke therapy

Statins (3-hydroxy-3-methylglutaryl (HMG)-coenzyme (Co) A reductase inhibitors), 3-hydroxy-3-methylglutaryl (HMG)-coenzyme (Co) A reductase is the rate-limiting enzyme in cholesterol formation in the liver. HMG-CoA reductase inhibitors (statins) lower serum cholesterol and especially lower the LDL component and may reduce the incidence of stroke; they include pravastatin, simvastatin, lovastatin, fluvastatin, atorvastatin, and cerivastatin. Hess et al. (125) reviewed several randomized trials of coronary artery disease and statins. Pravastatin lowered average cholesterol levels and reduced the risk of stroke in patients with coronary artery disease. Simvastatin reduced the risk of the combined endpoint of stroke and transient ischemic attack in hypercholesterolemia and coronary artery disease. The precise way in which statins reduce risk is unclear and may not be solely related to cholesterol or low-density lipoprotein reduction. Vaughan et al. (126) reviewed other important mechanisms: 1) nonsterol effects on vascular endothelial cells, 2) anti-inflammatory effects, 3) depletion and stabilization of the lipid core of plaques, 4) strengthening of the fibrous cap of plaques, 5) decreased formation of platelet–fibrin thrombi, 6) decreased deposition of clot on endothelial surfaces, 7) reduced thrombogenicity, and 8) anti-thrombotic effects on monocytes, platelets, and smooth muscle cells. Rosenson (127) proposed several mechanisms for cerebrovascular protection by statins. These mechanisms include reduction of cardiac, aortic, and carotid embolization sites; stabilization and reduction progression of vulnerable carotid atherosclerotic plaque; and improvement in cerebral blood flow. Statins also reduce the size of cerebral infarction in a murine stroke model, possibly via a neuroprotective effect.

Neuroprotection

Several treatments aimed at neuroprotection and salvation of ischemic neurons in stroke are being studied (128). A multitude of agents considered for study are listed in Table 1 (129). Lutsep and Clark (131) reviewed those treatments that have reached the late stage of development, including N-methyl-D-aspartate (NMDA)-receptor antagonists, antileukocyte antibodies (intercellular adhesion molecule (ICAM)-1 inhibitors), GABA agonists (clomethiazole), citicolen (phospholipid metabolism), opioid receptor antagonists (naloxone), and sodium channel blockers (fosprenyltox). Promising results have been reported in animal stroke models. Unfortunately, to date, there is no clear and convincing evidence in randomized controlled clinical trials to support efficacy in humans.

The North American Glycine Antagonist in Neuroprotection (GAIN) Investigators (132) reported on GV15/862, a selective blocker of glycine and an obligatory coagonist with glutamate of the NMDA receptor. This agent reduces infarct volume in rats with focal cerebral ischemia. Two randomized, double-masked, and placebo-controlled trials were reviewed, but no clinical conclusions could be drawn regarding efficacy.

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<td>Sodium channel blockers</td>
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Clomethiazole enhances gamma-aminobutyrate type A (GABA<sub>α</sub>) receptor activity. Efficacy and safety were tested in the Clomethiazole Acute Stroke Study (CLASS) (133). Investigators studied clomethiazole using a 24-hour infusion of 75 mg/kg versus placebo in 94 acute hemorrhagic stroke patients. The number of patients reaching functional independence on the Barthel index score (>60) was 59.6% for clomethiazole versus 53.2% for placebo. No substantial safety issues were raised.

Devuyst and Bogousslavsky (105) and De Keyser et al. (130) reviewed the discrepancy between experimental and clinical results for multiple neuroprotective agents, suggesting possible reasons: 1) single drug trials, 2) heterogeneity of stroke population, therapeutic dose, and adverse effects, and 3) therapeutic time window.

The role of neuroprotective agents in stroke remains to be defined.

PARANEOPLASTIC SYNDROMES

Paraneoplastic syndromes represent visual or neurologic dysfunction in the setting of known or suspected malignancies, without direct involvement of the eye or nervous system by tumor, antineoplastic agent toxicity, or opportunistic infection. They are thought to originate from an autoimmune process, and circulating antibodies to specific neuronal antigens have been identified in some cases. Syndromes of neuro-ophthalmologic significance primarily involve the retina, optic nerve, brainstem, and cerebellum. In this review, we focus on disorders of the retina and optic nerve (138–171).

Retina

Paraneoplastic retinopathies include primarily the cancer-associated retinopathy (CAR), melanoma-associated...
Antiretinal antibodies directed against other antigens have been detected in several recent reports of paraneoplastic retinopathy. Ohkawa et al. (144) described bilateral severe progressive retinopathy in a patient with endometrial cancer who demonstrated serum antibodies against only a 34-kd retinal protein. Autoantibodies to a 60-kd retinal protein were found in a patient with small-cell lung carcinoma with clinical and electrophysiologic features of CAR syndrome but negative testing for the 23-kd CAR antibody (145). Antibodies against the 46-kd protein enolase-a, a ubiquitous glycolytic enzyme (146) that is also elaborated by several tumor types, have been documented in patients with CAR. The antibodies were also detected in patients with vasculitis, other tumors without retinopathy, and in healthy patients, though the levels were lower. The enolase antibodies found in patients with retinopathy have also been shown to induce apoptosis in E1A.NR3 rat retinal cells, whereas those in healthy patients have not: the effect of these antibodies in vasculitis is unproven (147).

Progressive retinopathy resembling the CAR syndrome was reported by Mizener et al. (148) in two patients without malignancy during a 5- to 7-year follow-up period but with evidence of autoimmune disease and strong family history of autoimmune disease. Visual loss was unilateral and severe, with demonstration of a ring scotoma but normal fundus appearance. The ERG was flat in one case and, in the other case, showed evidence of inner retinal dysfunction with selective b-wave loss and abnormal oscillatory potentials. Circulating antiretinal antibodies reactive against the retinal inner plexiform layer but not against CAR antigen or other previously reported retinal antigens were identified. Whitcup et al. (149) reported a case of similar progressive retinopathy with severe depression of the rod-mediated ERG and antiretinal antibodies against recoverin, but no documented malignancy 3 years after onset of visual loss. They termed the disease recoverin-associated retinopathy. To distinguish it from the CAR syndrome, Keltner and Thirkill (150) further described the distinction in a separate editorial.

Management of CAR syndrome has generally been ineffective, but a benefit has been reported in certain cases, using systemic corticosteroids, plasmapheresis, or intravenous immunoglobulin (IVIg). Keltner et al. (151) described a patient whose antibody levels diminished and visual function improved and stabilized on corticosteroid therapy. More recently, Murphy et al. (152) described a patient in whom oral corticosteroid therapy combined with plasmapheresis resulted in recovery of vision. The vision improved from counting fingers to 20/200 OD and from 20/40 to 20/25 OS. This visual acuity was maintained at least 4 months with response of the tumor to chemotherapy and reduction of antiretinal (60-kd) antibody levels from 1 to 2000 to 1 to 200. Guy and Aptsiauri (152) reported response to IVIg (400 mg/kg/day during 5 days in one case and during 1 day in the other case) in two of three patients with paraneoplastic retinopathy. Visual acuity in the first case improved...
within 24 hours of the first dose from hand motions OU to 20/50 OD, 20/200 OS, with further improvement of OS to 20/40 after 72 hours. In the second case, visual acuity remained stable, but visual fields improved after the single dose.

Melanoma-associated retinopathy is a very rare visual paraneoplastic syndrome associated with cutaneous malignant melanoma, predominantly affecting men, though melanoma occurs relatively equally in men and women. In contrast to CAR, it is a disorder primarily of rods, with corresponding symptoms of photopsias, shimmering colored visual phenomena, and nystagmus, usually developing rapidly for weeks to months but occasionally with a sudden onset and eventually involving both eyes. The clinical examination often initially reveals normal visual acuity, color vision, and central visual field, with peripheral constriction, midperipheral scotomas, or generalized depression of the most common field abnormalities. Central scotomas are unusual. The fundus may be normal or may show RPE irregularity, retinal arteriolar constriction, and optic disc pallor in cases that have been symptomatic for months. Unlike the CAR syndrome, visual function may remain stable and nonprogressive in MAR. Visual symptoms typically develop in the setting of previously diagnosed melanoma, and metastasis is often found with the development of visual loss. No treatment has been proven effective for MAR (153–156).

The ERG abnormalities in patients with MAR syndrome suggest rod dysfunction, with severe impairment of the dark-adapted b-wave, sparing the a-wave response. Oscillatory potentials are reduced in a manner similar to other retinal disorders that are characterized by failure of neural transmission from outer to inner retina through the bipolar cell layer. Moreover, immunofluorescent staining of the retinal bipolar cell layer by circulating IgG autoantibodies has been demonstrated (154,157–159). Histopathologic evidence of dropout in the bipolar neurons of the inner nuclear layer of the retina has recently been documented by Gittinger and Smith (160). It is postulated that antimelanoma antibodies may cross react with these bipolar cells to produce the syndrome (155). The antigen is as yet unidentified, although a membrane-associated lipid is suspected. Lei et al. (161) demonstrated that intravitreal injection of circulating IgG antibodies from humans with MAR resulted in alteration of the dark-adapted b-wave of the monkey ERG, suggesting an autoimmune effect on the depolarizing subset of retinal bipolar cells.

Bilateral diffuse uveal melanocytic proliferation is a rare paraneoplastic disorder that has been reported in association with ovarian, lung, gall bladder, cervical, uterine, kidney, pancreatic, breast, esophageal, and colorectal cancers in more than half of the cases before identification of the underlying malignancy. Occasionally, the syndrome has developed coexistent with recurrence of a previously diagnosed tumor (162). There is a slight predisposition for women. Benign melanocytic proliferation and infiltration of the uveal tract is the characteristic feature. The syndrome presents with painless progressive bilateral visual loss over months, related to damage to retinal pigment epithelium and photoreceptors. Clinical findings include multiple reddish rounded spots at the level of the posterior retinal pigment epithelium—which are hyperfluorescent on angiography—multiple pigmented and nonpigmented focal melanocytic proliferations and diffuse thickening throughout the uveal tract, exudative retinal detachments, and rapidly progressive cataracts.

The differential diagnosis includes choroidal metastases, lymphoma, leukemia, sarcoidosis, uveitis, scleritis, uveal effusion, and Harada disease. Comparison and contrast to CAR were highlighted in recent reports by Brink et al. (163) and Gass (164).

Murphy et al. (165) recently described clinical features in a woman with uterine carcinoma who developed visual loss, exudative retinal detachments, and prominent conjunctival vascular dilation and tortuosity suggestive of arterialized blood vessels. The diagnosis of dural cavernous sinus fistula was considered, but cerebral angiography was negative, and she subsequently developed choroidal lesions typical for BDUMP. Conjunctival hyperemia and congestion has been reported in a number of previous cases, presumed secondary to ciliary body infiltration (166).

The pathogenesis of BDUMP is unknown. It has been suggested that retinal photoreceptor damage occurs because of toxic or immune factors independent of, or in response to, melanocytic proliferation, which may result from trophic hormone production by the tumor or from a coexistent oncogenic factor. Overexpression of p53 protein, a postulated mechanism for development of BDUMP, was not confirmed in recent studies by Margo et al. (167). There remains no effective treatment.

**Paraneoplastic optic neuropathy**

A syndrome of acute optic nerve dysfunction has been described in patients with carcinoma, particularly SCCL or lymphoma, in the absence of meningeal tumor infiltration; it is a presumed paraneoplastic neuropathy, although its etiology is unproven (168,169). Patients present with the rapid onset of progressive visual loss, usually bilateral, and in most cases associated with optic disc edema. Many of the reported cases also demonstrated brainstem and cerebellar dysfunction suggestive of a paraneoplastic syndrome. CSF analysis often shows mild to moderate lymphocytosis and elevated protein levels but no evidence of malignant cells. The ERG results are typically normal. Testing for CAR antibody is negative. At autopsy, most cases have shown demyelination in the affected tissues, associated with a perivascular lymphocytic infiltrate typical of findings in other paraneoplastic syndromes.

Luiz et al. (170) recently described a case of bilateral optic neuropathy and cerebellar degeneration in a 59-year-old woman eventually diagnosed with SCCL. She presented with acute bilateral painless loss of vision, optic disc edema, and severe visual field constriction, along with slurred speech, lower extremity weakness, ataxia, and other cerebellar signs. All testing results for brain
metastasis and meningeal infiltration was negative, although CSF lymphocytosis (122 WBC/mm$^3$) and elevated protein (111 mg/dl) were noted. ERG results were normal, and testing results for CAR, Yo, Hu, and Ri serum antibodies were negative. However, autoantibodies reactive against a 60-kd neural protein similar to that previously reported by Murphy et al. in a case of CAR-antibody-negative retinopathy with SCCL were present. These antibodies appear to react against antigens in the retina, optic nerve, cerebellum, and spinal cord, although a causative relation with the optic neuropathy has not been proven. Similar antibodies were noted by Malik et al. (171). The patient demonstrated prolonged visual improvement and stabilization at the 1-year follow-up examination after chemotherapy and pulse intravenous methylprednisolone.

Acknowledgment: This work was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc., New York, NY.

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Functional and Morphologic Comparison of Two Methods to Produce Transient Retinal Ischemia in the Rat

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Objectives: Much of our knowledge of the pathophysiology of retinal ischemic injury is from a multitude of studies that use in vitro or in vivo animal models of retinal ischemia followed by reperfusion. The objective of this study was to compare histopathologic and electrophysiologic (electroretinography) parameters using two different models of transient retinal ischemia: high intraocular pressure (HIOP) and suture ligation of the optic nerve (SL).

Methods: Transient retinal ischemia was induced using the HIOP model or the SL model in the Sprague-Dawley rat for either 30 or 60 minutes. Histopathologic outcome was determined at 1 and 7 days after ischemia. In addition, electroretinography (ERG) was performed at 2 hours, 1 day, 3 days, and 7 days after ischemia.

Results: At 1 and 7 days after 30 minutes of ischemia, there were no significant histopathologic abnormalities in the retina with either model, except for a slight decrease of the cell count in the ganglion cell layer (GCL) with the SL method. After 60 minutes of ischemia, there was significant thinning of the inner retina. There was a significant early dropout of cells at 1 day in the inner nuclear layer (INL) in the HIOP method compared to the SL method where the dropout was delayed and gradually progressive. Dropout of cells in the GCL was early (1 day) and gradually progressive in both models but more severe in HIOP than SL. There was a significant decrease in the ERG b-wave amplitudes as early as 2 hours after both 30 and 60 minutes of ischemia compared to preischemic baselines.

Conclusions: The degree of retinal injury after transient retinal ischemia was more severe at 1 day after reperfusion in the HIOP method compared to the SL method but was similar at 7 days in both models. Furthermore, our data suggests that functional assessment of ischemic damage by electroretinography may be a more sensitive parameter than conventional histopathologic quantification. The timing of either measurement relative to the ischemic stimulus is critical because histologic measurements performed too early after ischemia may underestimate the degree of injury.

Key Words: Ischemia—Retina—Rat—Suture ligation—High intraocular pressure.

Retinal ischemia may occur clinically in various settings, such as after acute retinal arterial occlusion, carotid artery disease, or other ocular disorders in which ischemia may play a pathogenetic role (e.g., diabetes mellitus, hypertension, or glaucoma) (1). Much of our knowledge of the pathophysiology of retinal ischemic injury is from a multitude of studies that use in vitro or in vivo animal models of retinal ischemia followed by reperfusion. In vitro models allow the opportunity to study separately hypoxia and substrate deprivation, the two major components of ischemia (2,3). However, interpretation of the results of these experiments is complicated by the contribution of toxic metabolic products and the inability to remove these products. In vivo models cannot separate the influence of hypoxia and substrate deprivation, and results may be strongly influenced by changes in blood flow (4,5). Nonetheless, in vivo models are of great significance and widely studied, because they are believed to be more representative of clinical disease.

Experimental studies have used such species as monkey (6), cat (7), rabbit (8), and rat (9–11). The use of less costly animals in the smallest number possible, while providing reproducible results relevant to human disease, is a goal of these studies. There are various practical and scientific advantages in the use of rats for these types of studies, and, as a result, many investigations of retinal ischemia involving this species have been reported (9,11–14). The rat retina is well vascularized (15), unlike that of other small animals such as rabbits (16), and is analogous to the human retina. In larger more costly animals such as cats, the functional recovery, especially in the early hours after ischemia, seems more robust (17). This observation is a disadvantage for designing experiments that seek to measure the degree of functional improvement after ischemia. Moreover, long-term follow-up after ischemia is more difficult and costly in such animal species. Despite the large number of earlier studies, the preferred method for inducing experimental ischemia in the rat retina in vivo is not known. At least four
different approaches have been described: 1) increase intraocular pressure (IOP) above systolic arterial blood pressure (9,10,18) (high intraocular pressure [HIOP] method), 2) ligation of the central retinal artery (9,11,19), including the optic nerve, using an occluding suture (SL), 3) a photothrombotic method (20), and 4) temporary carotid artery occlusion (21).

The photothrombotic method (20) is relatively simple, but it suffers from several substantial disadvantages: retinal damage is variable, perhaps because of different degrees of light exposure throughout the rat retina (20); the retina is inevitably detached (20); the injury itself resembles a complete infarction, producing widespread retinal necrosis (22); and because capillary thrombosis (the degree of which is not yet known) occurs (23,24), the model is that of permanent rather than reversible ischemic insult, effectively precluding the study of post-ischemic reperfusion events. Temporary occlusion of the carotid arteries (21) is simple to apply and is reversible, but its drawbacks include the need for extensive surgical exposure (invasiveness), effects of such ischemia on organs other than the retina (i.e., brain), and relative retinal sparing even in the presence of prolonged carotid occlusion. Because of these limitations, the photothrombotic and temporary carotid artery occlusion methods are less preferred in experimental studies of retinal ischemia. In contrast, the SL and HIOP methods are reversible, simple to apply, and require little specialized equipment or surgical manipulation. Because these two methods result in transient reversible ischemia, it seems more appropriate to extrapolate results from studies using these techniques to humans, because they more closely parallel the usual clinical situation. The major limitation in interpreting results using these techniques is that it is clinically unusual to find complete cessation of retinal flow in patients.

Although SL and HIOP methods produce ischemia by similar mechanisms, there has not been a previous controlled comparison of these two methods in the rat. Moreover, most previous studies have examined either electrophysiologic or histologic measurements of damage in isolation, and little data are available demonstrating electrical recovery over an extended period of time after ischemia. The purpose of this study was to determine the relative efficacy of the HIOP and the SL methods in studies of transient retinal ischemia and subsequent recovery in order to determine which of these two methods would be preferred in in vivo studies of retinal ischemia. Specifically, this study compares the histopathologic and electrophysiologic (electroretinography [ERG]) parameters using these two methods in the rat. Additionally, this study attempts to correlate retinal electrophysiology to histopathology subsequent to transient retinal ischemia.

METHODS

Animals and anesthesia

Procedures used in this investigation conformed to the Association for Research in Vision and Ophthalmology (ARVO) Resolution on the Use of Animals in Research and were approved by our animal care committee. We studied Sprague–Dawley rats, 150 to 200 gms, purchased from Taconic (Germantown, NY), maintained in a 12-hour on/12-hour off light–dark cycle. Animals were fasted overnight before surgery. The rats were anesthetized with an intraperitoneal mixture of ketamine 30 to 40 mg/kg and intramuscular xylazine 2.5 mg/kg injection. Adequacy of anesthesia was tested by tail clamping with a hemostat, and supplemental intramuscular doses of ketamine and xylazine were administered as needed. The rat was positioned prone during all of the measurements. Body temperature was maintained throughout all experiments at 37°C with a heating pad.

Induction of ischemia

High intraocular pressure method. This procedure has been described in detail previously (10). In brief, the anterior chamber OD was cannulated using a 27-gauge, ½-inch needle attached by a three-way stopcock to an infusion of sterile 0.9% saline and a manometer. Under direct vision, the needle tip was placed within the anterior chamber, and the corneal puncture site was sealed with cyanoacrylate cement. IOP was raised to 150 mm Hg in order to exceed systemic arterial blood pressure. After completion of the target period of ischemia, the needle was withdrawn and the IOP normalized.

Suture ligation method. We have described this procedure in recent publications (11,25–27). A sterile 2-0 suture was placed around the retrobulbar optic nerve and blood vessels OD, and the suture was pulled through a short length of polyethylene tubing (PE-200). By pushing the tubing toward the eye while clamping the suture to maximal tightness, we were able to produce complete ocular ischemia for the target period of time.

Complete loss of the electroretinogram b-wave as well as obliteration of retinal vessels by fundoscopic examination served as evidence of retinal ischemia in both experimental models. The contralateral eye of each animal served as a nonischemic control. One drop of gentamicin ophthalmic solution was applied topically to the ischemic eye before and after the eye was rendered ischemic.

Electroretinography

The procedures used were those we have previously reported (5,11,26). In brief, rats were dark-adapted overnight, their pupils dilated with tropicamide 0.5% and Cyclomydril (Alcon Laboratories, Inc., Ft. Worth, TX). A platinum electroencephalogram (EEG) electrode was placed on the topically anesthetized cornea, a reference electrode was placed on the ipsilateral mastoid, and a ground electrode was placed on the lower dorsum. The average response to 3 to 4 white-light flashes generated at a distance of 15 cm from the rat’s eyes was recorded. The ERG data were analyzed as previously described (5,11,26).

Light microscopy

The animals were anesthetized and the eyes enucleated at the chosen survival time points and then fixed in Trump fixative, consisting of 11.6 g of sodium...
monophosphate and 2.7 g of sodium hydroxide dissolved in 500 mL of distilled water, 100 mL of 37% formaldehyde, and 20 mL of glutaraldehyde, with further addition of distilled water to a volume of 1000 mL. Enucleated globes were then sectioned in the vertical meridian and the inferior portion of the eyeball (retina, choroid, and sclera) embedded in epoxy resin. One micron-thick sections were stained with 1% toluidine blue. The retinal hist架构ure was evaluated as previously described by light microscopy (10,11). Measurements of the thickness of the retinal layers were performed as follows: 1) outer limiting membrane (OLM) to inner limiting membrane (ILM), 2) outer nuclear layer (ONL), 3) outer plexiform layer (OPL), 4) inner nuclear layer (INL), and 5) IPL to ILM. The mean value for these measurements taken in four adjacent areas of the inferior retina within 1 mm of the optic nerve was calculated. Additionally, manual cell counts of the INL and ganglion cell layer (GCL) were performed over a length of 200 microns in the inferior peripapillary region of the retina. These measurements were performed in the same area of retina in all the eyes in order to prevent any effect on the results because of possible regional anatomic variation.

**Histopathology**

Each experimental group (HIOP or SL model) was divided so that the retina of each set of animals was rendered ischemic for 30 or 60 minutes. Repeat ERG examination was performed 2 hours, 1 day, 3 days, and 7 days after the end of 30 or 60 minutes of ischemia. These ischemic times were chosen on the basis of earlier studies that reported severe histologic damage after 60 minutes of ischemia in the rat and lesser degrees of damage after shorter periods of ischemia (9,14). Eyes were harvested for histologic examination at either 1 or 7 days after ischemia.

**Electrophysiology**

Both techniques produced reliable and reversible retinal ischemia. In the early postischemic period (first 2 hours of recovery) the b-wave recorded similarly in both models regardless of the duration of the ischemic insult. No significant changes in wave amplitudes were found over time compared to baseline in the nonischemic eyes of any of the groups. There was complete absence of ERG activity during ischemia and varying degrees of reappearance of the waveforms during recovery, depending upon the duration of ischemia. The b-wave amplitude increased throughout the recovery period, after 30 minutes of ischemia, to a final value of 74.9 ± 21.9% (p < 0.0095 vs baseline) at 7 days after ischemia for HIOP and 73.9 ± 7.1% for SL (Table 1).

In the 60-minute ischemic group, recovery of the b-wave plateaued by 120 minutes after ischemia ended, and the final value of 8.5 ± 2.1% (p < 0.00009 vs baseline) at 7 days after ischemia for HIOP and 11.7 ± 1.8% for SL did not differ significantly from values recorded at earlier recovery periods. The b-wave amplitude following 60 minutes of ischemia declined at 1 day, at a time when the histology only demonstrated mild histopathologic changes and remained depressed for up to 7 days (Table 1).

**RESULTS**

**Histopathology**

Ischemia sustained for 30 minutes using HIOP or SL resulted in no significant changes compared with the control in retinal thickness 1 or 7 days later. There was, however, a slight decrease in the GCL count at 7 days in the SL model. Ischemia sustained for 60 minutes using either HIOP (Figs. 1A, 1B, and 2) or SL (Figs. 1C, 1D, and 2) resulted in the typical histopathologic features expected subsequent to acute retinal ischemia (9,10,14). One day after ischemia, a decrease in the INL cell count was evident in the eye subjected to HIOP only, and a significant decrease in cell counts in the GCL in both models was noted (Fig. 1C, D). Light microscopy at 7 days after ischemia revealed similar histopathologic features in HIOP and SL models of retinal ischemia. There was a significant decrease in overall retinal thickness, with marked thinning of the inner retinal layers and extensive disorganization of the inner retinal hist架构ure (Fig. 1A, C). The number of cells in the INL and GCL of the ischemic retinas were reduced in both models (Fig. 1B, D). Of note, there was no further decline in the INL cell count after one day in the HIOP model as compared to the delayed decrease in the INL cell count that was seen 7 days after ischemia in the SL model.

There was slight thinning of the OPL 7 days after ischemia in the SL model only. The hist架构ure of the OPL showed disruption of the orderly, vertically oriented, columnar arrangement of cells and cytologic irregularities (Fig. 2).

**DISCUSSION**

The mechanisms of cell death caused by ischemia and reperfusion in the retina are not yet fully understood. The time course of postischemic neuronal damage in the retina is believed to be similar to that observed in other regions of the central nervous system. It appears that a
"maturation" phenomenon is present, whereby ischemic damage, at least according to histologic criteria, becomes more evident with increasing recovery times following ischemia. The initial ischemic insult results in cellular perturbations that continue to progress despite, or perhaps because of, reperfusion of the ischemic tissue (28). It is commonly accepted that ischemia and reperfusion lead to the generation of oxygen free radicals and excitatory amino acids, leading to cellular damage primarily from massive influx of Ca$^{2+}$. Ca$^{2+}$ influx results in the activation of enzymes such as lipases, proteases, endonucleases, nitric oxide synthase, and damage to cell membranes and DNA (4). Activation of these enzymes could lead to further increases in the production of damaging oxygen free radicals (29–32). Delayed cell death in the retina could also be the result of ischemia-triggered programmed cell death, or apoptosis; however, the mechanisms of this latter phenomenon remain to be determined (10,33–35).

The primary implication of the evolving injury after ischemia is that the extent of postischemic injury may be underestimated if examination is performed too early in the recovery period. In the present study, we have shown that the functional (ERG) and conventional histologic changes after ischemia progress over time and that ERG disturbance predate morphologic changes. In earlier studies, it has been shown that ganglion cell loss in the rat retina after ischemia increases with time (14). However, most studies examining retinal function (via measurement of the ERG) have confined measurements to the early hours after ischemia (36–39). Therefore, studies of the effects of various interventions on the outcome after a period of ischemia may yield deceptive information. In addition, the examination of either histologic or

**FIG. 1.** A,C: Measurements (mean ± standard error of mean [SEM]) of the thickness of retinal layers of nonischemic eyes (control), and eyes 1 day and 7 days after 60 minutes ischemia show a significant decrease in overall retinal thickness (OLM-ILM) and in the inner retinal layers (INL, IPL-ILM) in both the HIOP (A) and SL (C) models. B,D: Manual cell counts of the INL and GCL in control eyes and 1 day and 7 days after 60 minutes ischemia. The INL cell count is significantly reduced at 1 day in the HIOP model (B); a delayed decrease in the INL cell count is noted at day 7 in the SL model (D). The GCL cell count is significantly reduced at 1 day and 7 days in both the HIOP (B) and SL (D) models (n = 5 per group). *p < 0.05; †p < 0.01.
The present study provides new data showing simultaneously the functional and histologic progression of changes after retinal ischemia in the rat.

The duration of ischemia has a significant impact on postischemic recovery, and the results were similar using either model. After 30 minutes of ischemia with SL or HIOP, there was progressive b-wave recovery to nearly 75% of preischemic baseline 7 days later. However, 30 minutes of ischemia with HIOP or SL produced no significant retinal structural changes. These results could indicate that conventional light microscopy is not sensitive enough to detect changes in retinal structure. The findings are similar to those following 45 minutes of bilateral carotid artery occlusion in the rat (41) and are consistent with the lack of significant change in the number of retinal ganglion cells after 30 minutes of ischemia by increased IOP in the rat retina (14). Thus, 30 minutes of ischemia using either HIOP or SL may be a useful duration to examine the mechanisms responsible for recovery of retinal function after ischemia.

Both retinal structure and function were significantly altered after 60 minutes of ischemia. These functional alterations were evident immediately after ischemia and became increasingly evident over time. That functional alterations show a greater magnitude in comparison to conventional histologic changes (> 90% decrement in function compared to a 45% decrease in inner retinal thickness) suggests that ERG may be a more sensitive means of assessing the extent of retinal damage in these models.

Earlier reports using the HIOP method showed a greater susceptibility of the inner retina to damage compared to the outer retina (9,15,39,42). Our present study demonstrates that whereas the HIOP and SL methods of retinal ischemia result in inner retinal damage with relative sparing of the outer retina, the outer retina is more adversely affected in the SL model. The apparent selective vulnerability of the inner retina to ischemia as compared to the outer retina cannot be attributed to a pressure phenomenon, because even in the SL method, the inner retina showed greater histopathologic alteration than did the outer retina. Nor can this selective inner retinal vulnerability be attributed to alteration in retinal blood flow alone because diminution of the retinal and choroidal blood flows have been demonstrated to occur to a similar degree by HIOP in the cat and by SL in the rat (43). Other mechanisms, such as variation in glycogen stores or greater sensitivity to excitotoxic and apoptotic damage (10,35), may be involved.

The results of this study show remarkable similarity between the two commonly used experimental techniques, histopathologically as well as electrophysiologically. An earlier report comparing similar models in the cat demonstrated that HIOP led to greater injury than SL (44). There were, however, several important differences between that study and ours, including the use of cats in place of rats, a greater increase in IOP (to 160 mmHg), short-term follow-up of the ERG (only until 390 minutes postischemia), a greater degree of surgical manipu-
tion to produce ischemia with SL, and no histologic measurements. In conclusion, both SL and HIOP are suitable experimental models for the study of retinal ischemia in the rat, because ischemia is easily produced, reversible, and quantifiable by histologic or functional criteria. The combination of functional (ERG) and histologic quantification of ischemic damage is important in the evaluation of ischemic injury, because functional measurements may reveal injury at a time when retinal morphology appears relatively normal. Conventional histologic measurements performed too early after ischemia may underestimate the degree of injury. Thus, the timing of either measurement relative to the ischemic stimulus is critical in designing studies of retinal ischemia.

Acknowledgments: This work was supported by National Institutes of Health Grants EY11253 (DMR), EY10343 (SR), and Research to Prevent Blindness, New York, NY (PSR). We thank Ms. Antoinette Barneccott for her expert assistance in the preparation of this manuscript.

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Book Reviews


**Type of book:** This is an introductory level soft-cover handbook designed to serve as an overview of the basic diagnostic and treatment modalities of a common patient complaint—headache. It is part of a series titled "The most common complaints." The focus of the text is on enabling the reader to more accurately and quickly ascertain the cause of the patient's symptom and to facilitate more timely and appropriate care. A case-based format is used to successfully reach this goal.

**Scope of book:** This text is developed as an efficient guide, generating an appropriate differential diagnosis. Headaches are first categorized based on longevity of symptoms. The author organizes our thinking by characterizing headaches as acute, subacute, or chronic. In each section, further subcategorization proceeds to allow the clinician to differentiate among headaches resulting from inflammation, bleeding, or more systemic processes. For each variety of headache, the text offers an overview and clinical approach. Management options are then discussed with varying amounts of detail; chronic entities (migraine and cluster headaches) receive substantially more attention.

**Contents:** The book encompasses 26 concise chapters. Chapters are subdivided into three sections; each section contains an overview before covering specific disease entities. The acute headache section includes chapters surveying meningitis, subarachnoid hemorrhage, and hypertensive encephalopathy. The subacute headache section covers cerebral tumors, pseudotumor cerebri, ophthalmic zoster, temporal arteritis, and subdural hematoma. The chronic headache section contains 13 chapters thoroughly detailing migraines, cluster, and tension headaches, including separate chapters on abortive and preventative treatments.

**Strengths:** This text provides a practical, concise overview of common causes of headaches in a pleasant easy-to-read manner. I particularly enjoyed the coverage of migraine aura, feeling that the author labored to cover various manifestations diligently. Tables that add to the text and nicely summarize relevant clinical data are included. Each chapter is followed by a short bibliography of historical interest and timely update.

**Deficiencies:** The author presents treatment modalities based largely on his extensive experience. Whereas this focus may mostly be one and the same, it is a limited perspective. Much of the recommendations is problematic and not within the mainstream of what the practicing neuro-ophthalmic community might accept. For example, the author lists repeated lumbar puncture as "the treatment of pseudotumor cerebri," with the next step being a lumbarperitoneal shunt. Acetazolamide seems listed as an afterthought. There were also instances where more thorough discussion is warranted. The section on ophthalmic zoster minimizes the ophthalmic sequelae of herpes zoster virus (HZV) ophthalmicus. The illustrations are dated and the approach from the perspective of a neurologist rather than an ophthalmologist or neuro-ophthalmologist. It can easily fit in the pocket of a short white coat, but it will not be used by those professionals whose coats are longer.

**Recommended audience:** This text could serve as a useful starting point in the development of a solid knowledge base concerning this entity for medical students and junior residents in ophthalmology, neurology, internal medicine, and family practice. It will not be part of any neuro-ophthalmic library.

**Critical appraisal:** This work succeeds in its attempt to render the beginning student more adept in developing a thorough, relevant differential diagnosis when faced with this common complaint. Although it may be lacking in its coverage of treatment modalities, it does an excellent job in what we feel is its goal of introducing physicians in training to this disease group. It is headache 101, and an overview, at that.

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**Type of book:** This title is a multiauthored third edition of a text that began as a monograph in the late 1980s. It is partially driven by the National Neurofibromatosis Foundation, though dictated chiefly by the experience of the senior authors. It is packaged as a ready reference for the two separate neurofibromatoses we now recognize, NF1 and NF2. New contributors, including neurologists, geneticists, pediatricians, and pathologists, have been added since the second edition. Disappointedly, ophthalmologists are not among them.
Scope of book: The book is an overview of NF1 and NF2, with historical backgrounds, clinical and pathologic features, some molecular biology, and associated tumor-related conditions. In truth, it is 80% NF1 and 20% NF2. It is a book that is directed to the patient, as well as to the caregiver, and so it will be of some interest to families of patients, social workers, and pediatricians.

Contents: The book is divided into an introductory section that speaks to the historical background of NF1 and NF2. The sections on NF1 include epidemiologic features, evaluation of the patient, clinical genetics, structure and function of the NF1 gene, tumors associated with NF1, cognitive anomalies of such patients, abnormalities of the central nervous system, tumors of the visual pathways, other malignancies, skeletal system involvement, and vascular and endothelial abnormalities. There are many black and white photographs, some schematic diagrams, and occasional tables of interest and relevance. The section on NF2 is remarkably short, compassing three chapters and perhaps 60 pages. This section addresses clinical aspects of NF2, associated tumors, and molecular biology thereof. The book is characterized by an appendix of resources for patients and their families, with e-mail addresses, telephone numbers, and some lay references.

Strengths: The text is a casual summary of two diseases, but it is not directed toward the neuro-ophthalmologic community. The strengths of the text are its helicopter perspective, up-to-date molecular biology, simple discussions of structure and function, the genetic basis of these diseases, and a useful bibliography accompanying each chapter.

Deficiencies: The chapter on tumors of the optic pathway is cursory and lacks much of the subtlety that the neuro-ophthalmologic community is used to seeing—description of discs, fields, scans, and subtleties of clinical declarations. Many of the drawings are poorly reproduced and the bibliographies strikingly overlook the ophthalmology literature.

Recommended audience: This product is a book designed for those persons interested in the neurofibromatoses, yet not expert therein. It is a good reference for patients and family, social workers, pediatricians, and family practice doctors. It is not an encyclopedia, but serves as more than a picture book. It is intended to be a collection of clinical presentations centered on photographs, cartoons, line drawings, charts, graphs, and schematics. It is an overview of the basics of ophthalmology, presented as a series of wonderfully illustrated lectures. It is conceptualized as a framework on which the reader can build and add.

Critical appraisal: The book is a simple package of NF1 and NF2, their differences and similarities. It is simply written, simply presented, and timely in its information. It contributes to a topic that has changed more in the last 10 years than the previous 100 years. It will be of interest to medical students and the ophthalmology and neurology resident, and it continues the tradition of the previous two editions.

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Type of book: This title is a multiauthored atlas of ophthalmology contributed to by the faculty of the Bascom Palmer Eye Institute at the University of Miami, and their friends and former fellows from throughout the world.

Scope of book: The volume is an atlas first and foremost but serves as more than a picture book. It is intended to be a collection of clinical presentations centered on photographs, cartoons, line drawings, charts, graphs, and schematics. It is an overview of the basics of ophthalmology, presented as a series of wonderfully illustrated lectures. It is conceptualized as a framework on which the reader can build and add.

Contents: This book is organized into 15 sections, ranging from diagnostic examination and testing to sections encompassing all the subspecialty areas. Each section contains an average of seven chapters. The chapters begin with brief introductory summaries, followed by a wealth of images with detailed keys. There is an introductory text for each section, with virtually no free-flowing text thereafter; almost all narration is tied to the images. The flow is meant to simulate attendance at a lecture, where an image is projected and the speaker then uses that image as the foundation for the discussion. This concept is a novel and creative idea that succeeds well.

Strengths: The layout and flow, along with the extraordinary quality and volume of color reproductions, combined with the authors' insights and well-chosen words are this book's main strengths. Ophthalmology is a visual science in which images are worth more than words. A straight atlas, however, can sometimes leave the reader wanting more; this atlas is anything but that. The format of this text keeps the reader interested. Another strength lies in the relative comprehensiveness of the text; it is notable that a chapter on ocular surface reconstruction is included, detailing a topic such as amniotic membrane transplantation for limbal deficiency. From the neuro-ophthalmologist's perspective, the chapters on orbital disease are exceptional. Also commendable is the inclusion of extensive reference lists at the end of each chapter.

Weaknesses: There are no critical weaknesses to this book. In the chapter on medical therapy for glaucoma, the text lacked sufficient discussion of the varying opinions regarding which medications should be used first line and why, versus second line, etc. The sizes of the photographs were adequate. However, some of the fundus photographs in the vitreoretinal section are smaller than one might like.

Recommended audience: This volume can serve as a useful reference for medical students and ophthalmology residents in training. It can serve as a wonderful lecture series for students overseas. Because of its broad scope and wealth of information, it could also...
serve well as a general reference text for comprehensive ophthalmologists.

Critical appraisal: This title is an informative, interesting, and clinically relevant general atlas. It is an excellent introductory, yet fairly comprehensive, source for residents or practitioners who want a broad overview or a place to use as a starting point for answers to a wide range of clinical questions. This book does for the 21st century what Vaughan’s ophthalmology book of the Lange series did for past generations. It will have an important place in the library of the beginning ophthalmologist.

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European Literature Abstract

H. Estrel Killer, MD


The management of traumatic optic neuropathy (TON) is still controversial. The range of therapy includes decompression of the optic canal, optic nerve sheath fenestration, high-dose steroids, and doing nothing. Mariak et al. studied the effect of high-dose steroid therapy (20 mg of dexamethasone every 6 hours, tapered after 24 hours to 24 mg/d) in 15 patients with TON. The patients presented for follow-up examination 3 to 11 years after injury. In 6 patients, visual acuity was no light perception before and after treatment. In two patients, visual acuity improved from light perception to 5/50 (5/10, respectively), and in one patient visual acuity improved from light perception to 5/7 shortly after the treatment. At the last examination, however, only the patient with 5/50 vision remained stable, and the other two patients were back to light perception.

The result of this study seems to confirm that bad vision in patients with TON is a lasting problem, and that the improvement after steroid medication may be only of limited benefit.