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An Anisocoria Produces a Small Relative Afferent Pupillary Defect in the Eye With the Smaller Pupil

Byron L. Lam, MD, and H. Stanley Thompson, MD

Objectives: To determine whether an anisocoria can produce a relative afferent pupillary defect of clinical importance.

Material and Methods: Anisocoria and relative afferent pupillary defect were measured with infrared videography in three clinical experiments: 1) every few minutes in eight normal subjects who remained in darkness as one pupil was dilating from mydriatic drops; 2) every 2 hours, for 8 hours in six normal subjects who remained in room light after one pupil was dilated with mydriatic drops; and 3) before and after dilation of one pupil in 24 patients with known afferent defects from optic nerve disease and who remained in room light.

Results: In the presence of an anisocoria, the relative afferent pupillary defect was almost always in the eye with the smaller pupil. The results of the three experiments were: 1) In darkness, the induced pupillary defect was found to be related to the ratio of the areas of the two pupils (R = 0.942), and 0.14 log unit of pupillary defect was produced in the eye with the smaller pupil for every millimeter of anisocoria. 2) In room light, the induced pupillary defect was in the eye with the smaller pupil but was less than in Experiment 1 and persisted throughout the 8 hours. This was presumably because the eye with the larger pupil had become more light adapted in the clinical light than the eye with the smaller pupil. 3) In room light, inducing an anisocoria in patients with preexisting afferent pupillary defect tended to shift the pupillary defect toward the eye with the smaller pupil (R = 0.68).

Conclusions: Clinically, approximately 0.1 log unit of relative afferent pupillary defect is produced in the eye with the smaller pupil for every millimeter of anisocoria. Therefore, the anisocoria must be larger than 2 mm in diameter difference to induce a clinically significant relative afferent pupillary defect.

Key Words: Anisocoria—Afferent pupillary defect.

Whether an anisocoria can, all by itself, produce a significant relative afferent pupillary defect is important in situations in which visual loss and a large anisocoria occur together. For example, you are asked to examine a stuporous patient in the emergency room because his right eye has been injured. The pupil of the injured eye is dilated to 8 mm and unreactive to light, possibly because of a traumatic tridoplegia. Your immediate concern is whether the retina or optic nerve has also been injured. The other eye is uninjured and its 3-mm pupil seems to be reacting normally. You carefully compare the direct and consensual light responses of the left pupil and find them equal. Can you safely accept this as evidence that there is no traumatic right optic neuropathy? Or could the anisocoria be covering up a real afferent defect? The answer to this question may influence the decision to treat the patient with high-dose corticosteroids or to consider decompression of the optic canal.

An anisocoria would be expected to influence pupillary light reactions because the pupillary inequality allows more light to get into one eye than into the other. The difference in retinal illumination between the two eyes should be proportional to the difference in pupillary area. Thus, the retina of the eye with the larger pupil should receive more stimulus light while the pupils are being tested for a relative afferent pupillary defect. However, in ordinary ambient daylight, the retina of the eye with the larger pupil should become relatively more light adapted and therefore somewhat less sensitive to light than the other eye.

It has been clinically estimated that for each millimeter of anisocoria, approximately 0.1 log unit of relative afferent pupillary defect is produced in the eye with the larger pupil (1). This estimate was based on a few measurements of the effect of anisocoria on the Pulfrich illusion and the perception that, given its range of movement, the pupil is unlikely to change retinal illumination by more than 1 log unit. However, careful measurements have not been made in a clinical setting.

SUBJECTS AND METHODS

Three clinical experiments were performed, and in all instances, an anisocoria was induced by dilating one pupil with eye drops. The size of the pupils and the relative afferent pupillary defects were measured by using an infrared sensitive video system (2). The relative afferent pupillary defect was measured by watching the direct and the consensual responses of the undilated pupil that still had a working sphincter. This
was performed in a darkened room using a halogen transilluminator (No. 41100 Finhol; Welch Allyn, Skaneateles Falls, NY) at maximal brightness while the subjects looked at a distant target. Infrared-blocking filters were placed over the stimulus light to avoid washing out the video picture. Calibrated neutral density filters in 0.3 log unit steps were used to measure the afferent pupillary defect. To minimize variation in illumination, one observer alternated the light from eye to eye and kept the light approximately 4 cm from the iris and below the visual axis. At the same time, the other observer watched the pupillary responses on the screen and decided whether a dense enough filter had been used to reach the balance point. Sufficient filters were used to deliberately overshoot the balance point so that the true balance point could be determined later from the video tape to estimate the afferent pupillary defect by interpolation to the nearest 0.1 log units. Four to five additional alternations of the light stimulus were then made without the neutral density filters so that the anisocoria could be assessed without the filters in place.

Pupillary size measurements were made by affixing adhesive paper millimeter rules to each lower eyelid in the iris plane. Pupillary diameters were measured from the videotape by using a caliper on the video image of the pupil and reading off the millimeter scale below each eye. The diameters of the pupil in the horizontal and vertical axes were recorded, and the mean of these two diameters was used as the diameter of the pupil. The difference between the pupillary diameters was used as the anisocoria. The left pupil was measured just as the light was leaving the right eye and just before the stimulus light had reached the left pupil and vice versa; that is, in the middle of the 300 milliseconds required to move the stimulus light from one eye to the other, as the light crossed the nose. We did this because the pupil size at the moment that the light fell on the eye determined the retinal illumination and the resulting pupillomotor input. Pupillary diameters were also measured when the neutral density filters needed to balance the pupillary reactions were in place.

In Experiment 1, the afferent pupillary defect was measured at different levels of anisocoria during the process of unilateral pharmacologic mydriasis in darkness to determine whether an anisocoria can produce an afferent pupillary defect. Eight adults with normal eyes, equal pupils, and no afferent pupillary defect had their right pupil dilated with a mixture of tropicamide 0.5% and phenylephrine 5%. The subjects were not dark-adapted before the experiment, and the afferent pupillary defect was measured every few minutes as the right eye dilated. The session was terminated when the medecated eye reached peak mydriasis after 30 to 40 minutes.

In Experiment 2, the presence and persistence of an anisocoria-induced afferent pupillary defect in room light was studied. Six normal adults had their right pupil dilated with cyclopentolate 1% and phenylephrine 2.5%. The subjects were dark-adapted for 35 minutes to minimize any preexisting asymmetry of retinal photochemical adaptation. The subjects then returned to work in their usual indoor lighted environment. With the right pupil fixed in mydriasis, the anisocoria and the relative afferent pupillary defect were measured every 2 hours until 8 hours after dilation. Mydriatic drops were placed in the right eye a second time, 4 hours after the first drop to maintain the anisocoria.

In Experiment 3, the effect of an induced anisocoria on an existing afferent pupillary defect was studied. The afferent pupillary defect and pupil size were measured in 24 adult patients with preexisting afferent pupillary defects before and after dilating one eye with tropicamide 0.5% and phenylephrine 5%. During the 40 to 60 minutes of dilation, the patients sat in a well-lit waiting room. Any preexisting physiologic anisocoria was subtracted from the final anisocoria. The video segments were reviewed in a random order to determine the amount of the relative afferent pupillary defect for each patient. The results were masked and the videotape was reviewed again to measure the anisocoria.

RESULTS

In Experiment 1, the changes in the relative afferent pupillary defect during mydriasis were measured in darkness. The results of a typical subject are shown in Figure 1. The induced relative afferent pupillary defect was found in the eye with the smaller pupil, and there was a striking linear increase in afferent pupillary defect (in log units) with increasing anisocoria (in millimeters of diameter) for all eight subjects. The average number of data points contributed by each subject was 17 (range 10-22). The intercepts ranged from -0.13 to 0.05, the slopes ranged from 0.10 to 0.16, and the correlation coefficients ranged from 0.93 to 0.99. When the results of the eight subjects were combined (Fig. 2), the pooled estimate of the correlation coefficient (R) based on growth curve analysis (3) was 0.971; with the intercept at zero, the slope was 0.136 (p < 0.0001), indicating that each millimeter of anisocoria produced approximately 0.14 log units of pupillomotor input defect. When these data were plotted against the anisocoria measured with the balancing neutral filter in place and expressed as the ratio of the area of the larger pupil to the area of smaller pupil (Fig. 3), the results approached the theoretical expected values (see Discussion) with the pooled estimate of the correlation coefficient (R) of 0.942.

In Experiment 2, the changes in the relative afferent pupillary defect after mydriasis in room light were assessed. All six normal subjects had a relative afferent pupillary defect of less than or equal to 0.4 log units in the undilated eye after 2 hours in room light (Fig. 4). This small amount of pupillomotor input asymmetry persisted throughout the experimental period even though the mean afferent pupillary defect showed a slight but statistically significant decrease after hour 5 (p = 0.0006, analysis of variance). The mean decrease in the afferent pupillary defect throughout the course of experiment was only approximately 0.1 log unit and therefore of doubtful clinical significance. The anisocoria remained relatively
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constant during the experiment so that the variation of anisocoria was not the cause of the change in the afferent pupillary defect, \( p = 0.57 \) by analysis of variance with anisocoria as covariable).

In Experiment 3, the changes in the relative afferent pupillary defect after mydriasis in patients with existing afferent pupillary defects were examined. The changes in anisocoria in 24 patients were compared to the changes in afferent defect (Fig. 5). After dilation, the relative afferent pupillary defect showed a tendency to shift slightly toward the undilated eye. The correlation between the amount of change in relative afferent pupillary defect and the amount of change in anisocoria was low, \( R = 0.68 \) with linear slope = -0.074.

DISCUSSION

When a large anisocoria is found with a relative afferent pupillary defect, it is clinically important to decide how much of the pupillary defect is induced by the anisocoria. Of course, measuring the relative afferent pupillary defect is possible with only one working iris sphincter. The three clinical experiments in this study showed that an anisocoria produces a small afferent pupillary
The difference in pupillomotor input between the two eyes in a normal subject should be directly related to the difference in the illumination of the two retinas. Retinal illumination is expressed as the intensity of the stimulus light times the pupillary area. This means that assuming a constant intensity of the stimulus light, a constant state of retinal adaptation, and intact afferent pathways, the relative afferent pupillary defect should be related to the ratio of the pupillary areas. Because the relative afferent pupillary defect is measured in log units with neutral density filters, the theoretical relationship between the relative afferent pupillary defect (RAPD) and the anisocoria would be:

$$\text{RAPD} = \log \left( \frac{\text{Area of larger pupil}}{\text{Area of smaller pupil}} \right) \times \frac{\text{stimulus intensity}}{\text{stimulus intensity}}$$

where \( D \) = diameter of larger pupil, \( d \) = diameter of smaller pupil.

However, as the pupil increases in size, the Stiles-Crawford effect and the optical blur of the peripheral lens may affect the pupillomotor input by reducing the effectiveness of the eccentric rays entering the periphery of the pupil (4,5). In addition, in ordinary ambient daylight the retina of the eye with the dilated pupil should become relatively light adapted and less sensitive to light. This would tend to reduce the pupillomotor input asymmetry caused by the anisocoria.

In Experiment 1, we measured the amount of afferent pupillary defect induced by various amounts of anisocoria during the process of unilateral mydriasis in eight normal subjects. This experiment was performed in darkness without the influence of continuous ambient light. When the anisocoria measured with the neutral density filter in place (the one that balanced the pupillomotor input asymmetry) over the dilated pupil and expressed as area ratio was plotted against the afferent pupillary defect, the result approached the theoretical values expected from the difference in pupillary areas alone (Fig. 3). These pupillary measurements with the balancing filter in place represent the anisocoria at the moment the relative afferent pupillary defect was being measured. Of course, these anisocoria measurements with the filters in place were made under special conditions unavailable to the clinician. In the clinic, the pupils are usually measured in millimeters of diameter with a pupil gauge and in diffuse light bright enough to see the pupils. With this in mind, we also measured the anisocoria without any filters in front of the dilated eye. In these subjects, one pupil was dilated and fixed, and the stimulus light was alternated from one eye to the other. The mobile pupil of the undilated eye was measured in a freeze frame just before it had a chance to dilate in response to the removal of the light stimulus from the dilated eye. Therefore, the anisocoria measurements are similar to that which might have been obtained clinically in bright light. When this anisocoria was plotted against the induced relative afferent pupillary defect (Fig. 2), we found that 1 mm of anisocoria produced approximately 0.14 log units of afferent pupillary defect in the eye with the smaller pupil (\( R = 0.971 \)). This constant of 0.14 log units of pupillary defect/millimeter of anisocoria is influenced somewhat by the range of the pupil size in our subjects because the difference in retinal illumination between the two eyes is related to a difference in pupillary area rather than a difference in diameter, and the same diameter difference for small pupils represents a larger difference in area.
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Relative Afferent Pupillary Defect in Undilated Eye (log units)

Time After Dilation (hours)

Undilated Pupil Diameter (mm)  3.8  3.7  4.1  3.8  3.9  3.9  4.0
Mean Anisocoria (mm)  4.3  4.1  3.4  3.8  3.7  3.7  3.5
Mean Afferent Defect (log units)  0.28  0.32  0.29  0.28  0.18  0.18  0.19

FIG. 4. Results from Experiment 2. The relative afferent pupillary defects in six normal subjects with one dilated eye were measured after exposure to room light. The induced afferent pupillary defect was in the undilated eye and persisted for several hours.

In Experiment 2, the persistence and persistence of anisocoria-induced afferent pupillary defects in room light were demonstrated in six normal subjects (Fig. 4). The mean diameters of the undilated and dilated pupils were 3.9 mm and 7.7 mm, respectively, and were relatively constant throughout the 8 hours of the experiment. The induced afferent pupillary defects were 0.4 log units or less in the eye with the smaller pupil and persisted throughout the 8 hours. The amount of afferent pupillary defect was less than the 0.6 log units calculated from the above theoretical formula.

In Experiment 3, the effect of a change in anisocoria in room light on 24 clinical patients with known afferent pupillary defects was examined (Fig. 5). Again, after dilating one pupil, the asymmetry of the pupillomotor input tended to shift toward the undilated eye. Although this shift appeared to be greater in some patients than in other patients and the correlation coefficient was low (R = 0.68), the result nevertheless suggests that an anisocoria may modify an existing afferent pupillary defect.

The slope was $-0.074$, which means that approximately 0.08 log units of afferent pupillary defect was produced for every millimeter of anisocoria. This is again less than the 0.14 log units of pupillary defect/millimeter of anisocoria found in Experiment 1.

The anisocoria-induced afferent pupillary defects were smaller in Experiments 2 and 3 than in Experiment 1 and smaller than would be predicted from the theoretical relationship. We presume that this was because, in these two experiments, the subjects were in room light and the retina of the eye with the dilated pupil had become relatively light adapted and less sensitive to light than the undilated eye because more light had been entering the larger pupil. This would tend to reduce the pupillomotor input asymmetry caused by the anisocoria. Nevertheless, the anisocoria-induced relative afferent pupillary defect in all three experiments tended to be in the eye with the smaller pupil, suggesting that the difference in retinal illumination during the alternating light test is the more potent factor and that it more than compensates for any difference in photochemical light adaptation between the two eyes.

Experiments 2 and 3 indicate that, under clinical conditions, the afferent pupillary defect shifts <0.1 log unit.
FIG. 5. Results from Experiment 3. The change in anisocoria after dilating one eye was plotted against the change in the relative afferent pupillary defect for 24 patients with a preexisting afferent pupillary defect. The anisocoria tended to shift the relative afferent pupillary defect toward the undilated eye.

in the direction of the smaller pupil for every millimeter of anisocoria. By itself, a relative afferent defect of <0.3 log units carries little clinical weight. Therefore, only large amounts of pupillary inequality (>2 mm) need to be taken into account when trying to measure the afferent pupillary defect. For example, if one pupil is 9 mm wide and the other is 3 mm, a substantial anisocoria-induced afferent pupillary defect of approximately 0.6 log units should be expected in the eye with the smaller pupil. If, in this situation, no afferent defect is found, the implication is that there is an input defect in the eye with the dilated pupil.

The difference between the clinically measured anisocoria and the anisocoria during afferent pupillary defect measurement depends on many factors: whether it is the larger pupil or the smaller pupil that is fixed to light, whether it is the eye with the larger or the smaller pupil that has the input defect, the size of the input asymmetry, and the intensity of the light used while measuring the anisocoria and the relative afferent pupillary defect. In the clinic, the afferent defect is more often found in the eye with the large, poorly reactive pupil caused by injury, third nerve palsy, or previous eye drops. In these cases, the anisocoria varies with lighting conditions. The smaller mobile pupil will constric t more light enters the pupil, and the brighter the light the greater the anisocoria will be. However, in very bright light, the small pupil will "hit bottom" so that the anisocoria no longer increases with further increases in stimulus intensity (6). The act of measuring the afferent pupillary defect may also affect the anisocoria depending on whether the larger or the smaller pupil is fixed. In our experiments, when the balancing filter was in place over the dilated eye, the retinal illumination during the test was decreased by the filter and this reduced the anisocoria because with the smaller pupil mobile and the other pupil fixed in mydriasis, every further decrease of the light stimulus in the dilated eye caused less constriction of the smaller
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pupil and this decreased the anisocoria. Hence, the clinically measured anisocoria may be somewhat different from the anisocoria present during the alternating light test depending on the intensity of the stimulus. We would suggest that in the clinic, the pupil size is best estimated with a pupil gauge in moderately bright diffuse room light with the patient looking at a distant object. If in patients with dark irises, more light is needed to see the pupils, then further diffuse light can be shone obliquely on the eyes from below.

In conclusion, although there are many factors that may influence the amount of anisocoria-induced relative afferent pupillary defect, the results of this study indicate that an anisocoria produces a relative afferent pupillary defect in the eye with the smaller pupil, and clinically, about a decibel (0.1 log unit) of afferent pupillary defect is produced for every millimeter of anisocoria. Therefore, it takes a large anisocoria of >2 mm in diameter difference to induce a clinically significant relative afferent pupillary defect.

REFERENCES
Bedside Tests of Saccades After Head Injury

Lindsay E. Mulhall, Dip. App. Sc. (Orth), Isla M. Williams, M.D. F.R.A.C.P., and Larry A. Abel, Ph.D.

Objectives: To compare the techniques of bedside and infrared oculography tests of saccades and to compare the results of both tests in control subjects and in patients with traumatic brain injuries (TBI).

Materials and Methods: The authors elicited single memory-guided saccades, antisaccades, and self-paced saccades in 19 TBI subjects and 26 age-matched control subjects at the bedside. Taped instructions were used to ensure that the timing and sequence of each stimulus (index finger flexion) were the same in all subjects and as close as possible to those used in both the current and previous laboratory studies.

Results: Self-paced saccade rate was significantly decreased in patients with TBI. The increased error rate in single memory-guided saccades and antisaccades was not statistically significant.

Conclusion: The authors concluded that the bedside saccade tests have limited value in patients with TBI because of the range of results and large overlap of the distributions of these two groups. The number of parameters that can be measured is limited. Bedside saccade tests are easier than infrared oculographic tests because the target remains visible.

Key Words: Antisaccades—Eye movements—Memory-guided saccades—Self-paced saccades—Traumatic brain injury.

Survivors of severe nonmissile traumatic brain injury (TBI) have widespread cerebral damage with lasting neurologic and cognitive dysfunction. Using infrared oculographic (IRO) tests, we showed that patients recovering from severe TBI have a decreased self-paced saccade rate, impaired ability to suppress inappropriate saccades in single memory-guided and antisaccade tests, prolonged saccadic latencies, and hypometric saccades in the visually guided reflex saccade tests (1). All saccades (except the fast phases of nystagmus) are triggered by structures within the cerebral hemispheres (2). Saccades under different behavioral circumstances are controlled by different cortical and subcortical areas (2).

Many patients who have sustained severe TBI have other injuries that will not allow recording of eye movements with IRO in the laboratory. In the current study, we recorded voluntary control of saccades at the bedside, using tape-recorded instructions that ensured that stimuli appeared with the same timing and sequence as in the laboratory IRO tests. The testing paradigms at the bedside resembled, as closely as possible, the paradigms used in the laboratory (1). Our aims were to compare the bedside saccade testing with tests in the laboratory using IRO and to compare their results.

METHODS

Subjects

Patients participating in the current study had sustained a severe nonmissile traumatic brain injury and had been admitted to Bethesda Hospital, Melbourne, for rehabilitation. We excluded subjects with clinically detected impairment of vision that would affect their ability to do the tests. No patients had a visual field defect that would affect their ability to fixate on targets presented and none had neglect. We excluded subjects with clinically apparent nystagmus or third- or sixth-nerve palsy. Also excluded were patients with a history of neurologic or psychiatric disturbance and those who could not satisfactorily perform the simple visually guided saccade tests. Three of the patients were taking carbamazepine prophylactically. Our previous study of saccades in patients with head injuries showed that carbamazepine did not significantly influence our results (1).

All patients included in the study had been injured in motor vehicle accidents, and most had multiple injuries that prevented their attendance at the laboratory for testing. The 19 patients aged 18 to 40 years (mean, 24.6 years, SD, 4.9) were examined within 5 months of the head injury. All had posttraumatic amnesia (PTA) for more than 7 days (range, 8–70 days; mean, 32.1, SD, 20.3), and were therefore classified as having very severe head injuries according to Russell and Smith (3). All patients had emerged from PTA at least 7 days before testing. Posttraumatic amnesia duration was determined using the Westmead PTA scale (4). Clinical details and the results of computed tomography imaging are summarized in Table 1. Five patients were retested 6 months after the first examination. Twenty-six control subjects aged 19–43 years (mean, 28 years, SD, 7.1) were tested.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/sex</th>
<th>PTA days</th>
<th>Days post injury</th>
<th>GCS on first admission</th>
<th>Clinical findings at time of testing and relevant immediate past history</th>
<th>CT reports</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26 M</td>
<td>70</td>
<td>144</td>
<td>7</td>
<td>Needed a lot of practice; R hemiparesis, bilateral foot drop; entropion, entropion; upper extremity paralysis; right side, mild ataxia; characteristic; benign nystagmus; right side</td>
<td>Multiple small pericerebral hemis in posterior L temporal, parietal and limb; and L frontal lobes. Soft tissue swelling in frontal and parietal lobes.</td>
<td>Indomethacin</td>
</tr>
<tr>
<td>2</td>
<td>23 F</td>
<td>63</td>
<td>74</td>
<td>8</td>
<td>ALERT, cooperative; L SOA, OSA, R hemiparesis; R maxillary sinus</td>
<td>Multiple central contusions</td>
<td>Ethinylcysteine</td>
</tr>
<tr>
<td>3</td>
<td>22 M</td>
<td>60</td>
<td>78</td>
<td>8</td>
<td>ALERT, cooperative; L SOA, OSA, R hemiparesis; R maxillary sinus</td>
<td>Bilateral frontal lobe contusions; greater in L; soft tissue swelling over R posterior frontal parietal region.</td>
<td>Ethinylcysteine</td>
</tr>
<tr>
<td>4</td>
<td>25 F</td>
<td>56</td>
<td>106</td>
<td>7</td>
<td>Needed repeated instructions; L foot drop</td>
<td>Preepenemic hem.</td>
<td>Amoxycillin</td>
</tr>
<tr>
<td>5</td>
<td>18 M</td>
<td>56</td>
<td>101</td>
<td>9</td>
<td>ALERT, talkative, longstanding ET, L amblyopia, Occipital LIO, FInd horizontal jerk nystagmus on R gume.</td>
<td>No abnormality detected.</td>
<td>Amoxycillin</td>
</tr>
<tr>
<td>6</td>
<td>19 M</td>
<td>48</td>
<td>80</td>
<td>3</td>
<td>Poor concentration, needed repeated instructions; R homonymous hemianopia, right quadrant visual field defect, dysphoria, dyscalculia.</td>
<td>Initially no abnormality detected, 2 weeks postinjury hydrocephalus, 5 weeks postinjury limited cerebral atrophy, left ventricle mildly enlarged, temporal horns enlarged, large cystic lesion. 16 months postinjury. Extensive areas of atrophy in L parieto-temporal cortex, mild ventriculomegaly, poor gray/white differentiation, R intraventricular hem.</td>
<td>Indomethacin</td>
</tr>
<tr>
<td>7</td>
<td>18 M</td>
<td>47</td>
<td>73</td>
<td>3</td>
<td>Distastinable; dysphonia; sensory impairment L median nerve distribution; mild papules of SOA and RM. 3 days postinjury R frontal/polar cranial tension for raised ICP.</td>
<td>Traumatic pneumocephalus, fracture of splenoid, R orbit and frontal sinus.</td>
<td>Fludrocortisone</td>
</tr>
<tr>
<td>8</td>
<td>26 M</td>
<td>35</td>
<td>61</td>
<td>5</td>
<td>ALERT, talkative, well controlled accommodative effort.</td>
<td>Hem—R frontal and L frontal horn of lateral ventricle.</td>
<td>Fludrocortisone</td>
</tr>
<tr>
<td>9</td>
<td>22 M</td>
<td>23</td>
<td>27</td>
<td>14</td>
<td>ALERT, cooperative; L cervicothoracic and L parietal lesions.</td>
<td>Hem in R frontal and L frontal horn of lateral ventricle.</td>
<td>Fludrocortisone</td>
</tr>
<tr>
<td>10</td>
<td>22 M</td>
<td>21</td>
<td>47</td>
<td>3</td>
<td>ALERT, cooperative; mild R VII nerve palsy, cerebellar ataxia.</td>
<td>Hem in R frontal and R temporal lobes and intraventricular hematoma.</td>
<td>Fludrocortisone</td>
</tr>
<tr>
<td>11</td>
<td>24 f</td>
<td>21</td>
<td>40</td>
<td>3</td>
<td>ALERT, cooperative, needed reminders; mild R hemiparesis, mild R UMN facial palsy.</td>
<td>Hem—R intracerebral small L basal ganglia, posterior superior pole.</td>
<td>Fludrocortisone</td>
</tr>
<tr>
<td>12</td>
<td>24 f</td>
<td>19</td>
<td>49</td>
<td>3</td>
<td>ALERT, cooperative, R brachial plexus lesion.</td>
<td>R frontal contusions and intraventricular hem.</td>
<td>Fludrocortisone</td>
</tr>
<tr>
<td>13</td>
<td>31 M</td>
<td>16</td>
<td>62</td>
<td>7</td>
<td>ALERT, cooperative; X’; nystagmus on extreme R gaze, convergence 8 cm, bilateral idiopathic hemianopia.</td>
<td>Hem in corporo calcarine and L lateral ventricle.</td>
<td>Fludrocortisone</td>
</tr>
<tr>
<td>14</td>
<td>23 M</td>
<td>15</td>
<td>24</td>
<td>11</td>
<td>ALERT, talkative; R optic nerve lesion.</td>
<td>Intracerebral hematoma—bilateral, L frontal, L extra capsule, R basal ganglia. Hem sprout canal 18. Unexplained fracture of floor of R orbit.</td>
<td>Fludrocortisone</td>
</tr>
<tr>
<td>15</td>
<td>25 M</td>
<td>14</td>
<td>58</td>
<td>11</td>
<td>ALERT, cooperative, amnesia, R pupil larger than L (cause uncertain).</td>
<td>Moderate cerebral oedema resolved 2 days postinjury.</td>
<td>Fludrocortisone</td>
</tr>
<tr>
<td>16</td>
<td>21 M</td>
<td>14</td>
<td>63</td>
<td>7</td>
<td>ALERT, cooperative; mild L TRP, dysphoria, mild bilateral impairment of coordination.</td>
<td>Intracerebral hematoma—Coning—R frontal and L temporal lobes, fracture Rygomatic arch, R propius.</td>
<td>Fludrocortisone</td>
</tr>
<tr>
<td>17</td>
<td>25 M</td>
<td>14</td>
<td>100</td>
<td>7</td>
<td>ALERT; lesions R axillary, radial and ulnar, brachial plexus, Repetitive L arm movement on prolonged upgaze.</td>
<td>No abnormality detected.</td>
<td>Fludrocortisone</td>
</tr>
<tr>
<td>18</td>
<td>24 M</td>
<td>11</td>
<td>106</td>
<td>13</td>
<td>ALERT, talkative, positive Lhemiatet’s sign.</td>
<td>No abnormality detected.</td>
<td>Fludrocortisone</td>
</tr>
<tr>
<td>19</td>
<td>40 M</td>
<td>8</td>
<td>7</td>
<td>12</td>
<td>ALERT; previous CSE/CT, bilateral, Unsteady hand, broad based gait, slowed speech, Nystagmus on extreme L gaze.</td>
<td>No abnormality detected.</td>
<td>Fludrocortisone</td>
</tr>
</tbody>
</table>

Note: peripheral injuries other than to the nervous system have been omitted.

Amoxycillin: amoxicillin trihydrate; Bilat.: bilateral; CBZ: carbamazepine; CSF: cerebrospinal fluid; CT: computed tomography; E: esophoria; ET: esotropia; ETOH: ethyl alcohol; ET: entropion; ETOH: ethyl alcohol; ETOH: esophagial reflux; GCS: Glasgow Coma Scale; H: hemorrage; ICP: intracranial pressure; Indometh., indomethacin; L: left; R: right; LIO: left inferior oblique; LMR: left medial rectus; LPR: left lateral rectus; N: nerve; nerves: OKN, Optokinetic nystagmus; Par + Cod: Paracetamol + Codeine phosphate; Paracet: Paracetamol; Poloxal: Poloxalkol; PTA: posttraumatic amnesia; RM: right medial rectus; RSO: right superior oblique; LIO: left superior oblique; SWI: square-wave jerks; UL: upper limb; LRL: lower limb; UMN: upper motor neuron; LMN: lower motor neuron; X’: exophoria at 33 cm.
and 12 control subjects were reexamined approximately 6 months after their original tests.

**Procedure**

In this study, we have referred to all clinical saccade tests as bedside saccade tests. Informed consent was obtained from all subjects. Test protocols were approved by the Research and Ethics Committees of Bethesda Hospital and Monash University.

Each subject was tested with the following: cover-uncover and alternate cover tests at near and distance, visual acuity at near, ocular movements, convergence, confrontation fields with a red hat pin, and pupil reactions to light. Patients were tested seated, except Patient 14, who was tested lying supine. Only Patient 8 needed spectacles for testing, because he had a well-controlled accommodative strabismus.

The examiner sat or stood in front of the subject with her hands equidistant from the midline at approximately 20 degrees. She wore an earpiece and flexed the right or left index finger in response to the timed instruction from the audio tape. In the self-paced saccade test the earpiece was removed so that the subject and examiner could both hear the start and stop instructions. The timing and sequence of each test were as close as possible to those previously (1). When the subjects were reviewed at 6 months, the examiner was unaware of these subjects' previous tests, and to continue until the stop instruction (30 seconds after the start). The examiner counted the errors.

4. **Self-paced saccades.** The examiner and subject both listened to the taped start and stop instructions. Subjects were instructed to look at the examiner's nose and, at the start instruction, look back and forth as rapidly and accurately as possible between the examiner's two index fingers (held stationary in the same positions as for previous tests), and to continue until the stop instruction (30 seconds after the start). The examiner counted the number of refixations.

In the laboratory, five control subjects performed the bedside tests, followed immediately by the laboratory version of the tests in which light-emitting diodes replaced fingers as the target; a beep replaced the “go” instruction; and the eye movements were monitored by IRO. These tests and equipment have been described previously (1). When the subjects were reviewed at 6 months, the examiner was unaware of these subjects' previous scores.

Percentage error scores were calculated for single memory-guided and antisaccade tests (number of errors/number of finger flexions × 100).

**TABLE 2. Results of bedside eye movement tests at initial assessment of patients with head injuries and control subjects**

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Patients with head injuries n = 19</th>
<th>Control subjects n = 26</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% errors</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Memory-guided saccades</td>
<td>4.37 (4.58)</td>
<td>4.01 (6.71)</td>
<td>0.249</td>
</tr>
<tr>
<td>Antisaccades</td>
<td>3.78 (3.84)</td>
<td>2.67 (5.96)</td>
<td>0.350</td>
</tr>
<tr>
<td>Saccades in 30 secs</td>
<td>61.05 (12.66)</td>
<td>70.01 (13.88)</td>
<td>0.032*</td>
</tr>
</tbody>
</table>

*p < 0.05.

**FIG. 1. Scattergram showing self-paced saccade rate of 19 traumatically brain-injured subjects and 26 control subjects at initial assessment.**

![Scattergram showing self-paced saccade rate of 19 traumatically brain-injured subjects and 26 control subjects at initial assessment.](image)

**FIG. 2. Scattergram showing single memory-guided saccade percent error rate of 19 traumatically brain-injured subjects and 26 control subjects at initial assessment.**

![Scattergram showing single memory-guided saccade percent error rate of 19 traumatically brain-injured subjects and 26 control subjects at initial assessment.](image)
RESULTS

The mean self-paced saccade rate was significantly lower in the patients with head injuries \( (p = 0.032) \) (Table 2), but the scatter plot (Fig. 1) shows that the range is similar in TBI subjects and control subjects.

The TBI subjects had a slightly greater mean error rate than control subjects in both the single memory-guided saccades and antisaccades, but the difference did not reach statistical significance (Table 2). The range was similar in both groups, but a greater proportion of control subjects made no errors (Figs. 2 and 3).

Five control subjects came to the laboratory. The self-paced saccade rate was similar using LEDs or fingers as targets. The control subjects made more errors in the laboratory tests of single memory-guided saccades and antisaccades than in tests using fingers as targets, but the difference was not significant \( (\text{paired} \ t \text{ tests} \ p = 0.01) \) and prolonged average fixation time between saccades (359.57 msec, +/-153.53, control subjects 287.71 msec, +/- 48.35, \( p = 0.115 \)), the latter suggesting impaired disengagement. At the bedside, prolonged average fixation time appeared to be the major factor slowing the self-paced saccade rate, but the multiple steps (1.493 steps, +/-21, control subjects 1.295, +/-0.14, \( p = 0.01 \)) and prolonged average fixation time between saccades (359.57 msec, +/-153.53, control subjects 287.71 msec, +/- 48.35, \( p = 0.115 \)), the latter suggesting impaired disengagement. At the bedside, prolonged average fixation time appeared to be the major factor slowing the self-paced saccade rate, but the multiple steps were not seen easily. The bedside self-paced saccade rate and the IRO self-paced saccade rate were similar, because the two stimuli were constantly present in both tests.

In the self-paced saccade test, the subject fixated a target, disengaged fixation, generated a saccade to the

| TABLE 3. A comparison, using paired t tests, of the results of eye movement tests in control subjects at the bedside and in the laboratory (IRO) |
|-----------------|-----------------|-----------------|-----------------|
|                 | Bedside         | Infrared        |                 |
|                  | Controls n = 5  | Controls n = 5  | p-value         |
| % errors         | Mean (SD)       | Mean (SD)       | 2-tailed t test |
| Memory guided    | 4.76 (3.37)     | 12.33 (7.4)     | 0.144           |
| Antisaccades     | 1.38 (2.8)      | 6.67 (5.26)     | 0.489           |
| Saccades in 30 sec | 73.4 (11.65)   | 70.6 (9.29)     | 0.40            |
| IRO,             |                 |                 |                 |

FIG. 3. Scattergram showing antisaccade percent error rate of 19 traumatically brain-injured subjects and 26 control subjects at initial assessment.

DISCUSSION

Cerebral damage sustained by patients after severe TBI is widespread \( (5-7) \). All patients included in this study had a PTA for more than 7 days (Table 1) and therefore were judged to have sustained severe TBI (3).

Both the current study and the 1994 study (1) showed that patients after TBI had a low self-paced saccade rate, but this had improved slightly at the 12-month review in the 1994 study. The IRO study (1) demonstrated the low self-paced saccade rate was caused by both multiple saccades (359.57 msec, +/-153.53, control subjects 287.71 msec, +/- 48.35, \( p = 0.115 \)), the latter suggesting impaired disengagement. At the bedside, prolonged average fixation time appeared to be the major factor slowing the self-paced saccade rate, but the multiple steps were not seen easily. The bedside self-paced saccade rate and the IRO self-paced saccade rate were similar, because the two stimuli were constantly present in both tests.

In the self-paced saccade test, the subject fixated a target, disengaged fixation, generated a saccade to the

| TABLE 5. A comparison, using paired t tests, of the results of bedside eye movement tests in control subjects at initial assessment and at 6 months |
|-----------------|-----------------|-----------------|-----------------|
|                 | First visit n = 12 | 6-month review n = 12 | p-value |
| % errors         | Mean (SD)       | Mean (SD)       | 2-tailed t test |
| Memory guided    | 2.86 (4.91)     | 3.57 (3.59)     | 0.710           |
| Antisaccades     | 1.61 (2.98)     | 2.08 (2.43)     | 0.665           |
| Saccades in 30 sec | 68.6 (12.31)   | 74.08 (7.91)    | 0.097           |
| Self-paced       |                 |                 |                 |

TBI, traumatic brain injury.
other target, fixated, and disengaged fixation repeatedly for 30 seconds. The pathways following these eye movements are diverse (8-12) and, in our subjects, included the striate cortex, because the subjects were fixating visible targets. The cerebral control of single memory-guided saccades and antisaccades involves widespread cortical and subcortical structures, including the frontal eye fields, dorsolateral prefrontal cortex, and substantia nigra. These mediate the maintenance of fixation and the initiation of the volitional saccades (2,9,13-16).

To allow comparison of the bedside saccade test with the IRO saccade test, taped instructions for the examiner were designed to reproduce, as closely as possible, the timing and sequence of stimuli in the laboratory. Taped instructions provided precise timing of the self-paced saccade test.

Patients with TBI had a greater error rate than did control subjects in single memory-guided saccade and antisaccade tests. The difference was statistically significant in IRO tests (1) but not at the bedside. We suggest that the bedside saccade tests were easier. At the bedside, the subject suppressed an eye movement to a visible target and instead made a saccade to a still visible finger—afer an auditory cue in a single memory-guided saccade or, to an opposite finger, when the other finger flexed in the antisaccade test. In the laboratory, the subject suppressed an eye movement to look at a point where he remembered the light to have flashed (single memory-guided saccade test) or to a point in an equal and opposite direction to the light that flashed (antisaccade test). The five control subjects also found the bedside single memory-guided test and antisaccade test easier. The error rate was greater in the laboratory than at the bedside (Table 3). In each of the tests, the range of results was similar for patients and control subjects, but a greater proportion of control subjects had lower error rates (Figs. 2 and 3).

Currie et al. (17) first described clinical antisaccade tests in the assessment of dementia. They found that the antisaccade error rates correlated strongly with the severity of dementia in Alzheimer’s disease and, furthermore, patients with pseudo dementia had normal clinical antisaccade error rates. In our laboratory study of patients with TBI, we found that the impaired ability to suppress inappropriate saccades in single memory-guided tests and antisaccades was more sensitive in identifying impairment of goal-directed behavior than were the neuropsychologic tests (1). We found the self-paced saccade test results correlated with tests requiring visual scanning. Although the reduced self-paced saccade test results at the bedside were statistically significant, we do not recommend the clinical use of the test in patients with TBI, because of the broad and overlapping range of results in each group.

Using the bedside saccade tests, we can measure error rate but not latency. In the previous study in 1994 (1), latency in memory-guided saccades and antisaccades significantly separated control subjects and patients with head injuries and showed significant improvement in TBI subjects. The simple visually guided saccades at the bedside were not analyzed, because bedside tests could not measure latency, accuracy, and number of steps per saccade, factors that significantly separated control subjects and patients with head injuries in the previous study but that did not show improvement over time in patients with TBI.

The current study is a cautionary tale. At the bedside, the range of results and intersubject variability reduced the usefulness of these clinical tests in this population. Figures 2 and 3 show that the range of scores was similar for patients and control subjects, although a greater number of control subjects had no errors. Intersubject variability can be seen in Figs. 2 and 3. For example, in the memory-guided saccade test, 14 control subjects made no errors; however, 1 control subject had an error score of 24% and another had 19%. In antisaccades, 16 control subjects made no errors and 1 had an error score of 12%. The range of results with IRO in the previous study (1) was also large, but the overlap between patients with TBI and control subjects was less.

Only five patients with head injuries returned for review at 6 months; the mean results of single memory-guided saccades and antisaccades improved (Table 4), but because of the small numbers and intersubject variability, the improvement did not reach statistical significance. Twelve of the control subjects were reviewed at 6 months (Table 5). The statistics indicated that the control subjects’ self-paced saccade rate improved more than that of the head-injured patients, suggesting that improvement in these tasks may reflect practice effects rather than clinical recovery.

We conclude that, in patients with TBI, bedside saccade tests have limited value, but the limitations might be less in another patient group with less diffuse neuropsychology. In contrast, the IRO tests of saccades in patients with TBI in the laboratory produced results that correlated with neuropsychologic test results, and, furthermore, suppression of inappropriate saccades was more sensitive in identifying impairment of goal-directed behavior than were the neuropsychologic tests.

Acknowledgments: The authors gratefully acknowledge support by the Brockhoff Foundation and help from Dr. John Olver, Mrs. Lyn Stansbury and the staff of the Bethesda Hospital, and Mrs. Karen Gibson and Mr. Michael Gorman.

REFERENCES


Latent and Congenital Nystagmus in Down Syndrome

Lea Averbuch-Heller, M.D., Louis F. Dell'OssO, PhD, Jonathan B. Jacobs, M.S., and Bernd F. Remler, M.D.

Objectives: Although nystagmus has been reported in Down syndrome (DS), it has been poorly characterized, because most investigators have relied on clinical observations rather than on eye movement recordings. This study was conducted to investigate nystagmus in DS, using quantitative measurements of eye movements. Methods: Ocular motility and visual functions were examined in 26 unselected adults with DS and compared with those in an age-matched group of 35 subjects with other causes of mental retardation. The eye movements of those with clinically evident nystagmus were recorded with the infrared technique. We also recorded the eye movements of a child with DS and nystagmus. Results: Nystagmus was identified in six (23%) adults with DS and in none in the control group. All six patients showed latent/manifest latent nystagmus (LMLN), prominent with the covering of one eye, and esodeviation from 10 to 30 prism diopters. Eye movement recordings confirmed LMLN with its exponentially decaying waveform. Frequencies ranged from 2 to 5 Hz and amplitudes from 5° to 20°. While attempting to fixate straight ahead in the absence of visual cues, three subjects exhibited shifts in the mean eye position. In contrast with the findings in adults, the only child with DS examined had both congenital nystagmus and LMLN waveforms. Conclusions: The predominant type of nystagmus in the study subjects with DS is LMLN. The high prevalence of LMLN may reflect abnormal integration of visuospatial information that is typical of DS. The concurrent presence of congenital nystagmus in a child but only LMLN in the adults with DS raises the possibility of age-related waveform changes or could reflect sample variation.

Key words: Congenital nystagmus—Down syndrome—Latent nystagmus.

The cause of nystagmus in subjects with Down syndrome (DS) is unclear. Several investigators have found increased occurrence of nystagmus in DS, ranging from 5% to 30% (1-4). However, the true prevalence of nystagmus in DS is unknown because of the selection bias in many reports in which patients are recruited from ophthalmology clinics (2,5). Moreover, the type of nystagmus in DS has been insufficiently characterized, because most investigators have relied on clinical observations rather than quantitative oculography; when the latter was used, latent nystagmus (LN) was identified in some patients (5). In this article, we use the more encompassing term, latent/manifest latent nystagmus (LMLN) for this type of nystagmus and either LN or MLN to describe the nystagmus under monocular (one eye covered) or binocular (both eyes open) viewing. Although LMLN is also congenital and is present at birth, it is different mechanistically, in waveforms, and clinically from congenital nystagmus (CN).

Pathogenetic mechanisms of some forms of nystagmus with onset in childhood are still poorly understood. One form for which several mechanisms have been proposed is LN. LN may result from an imbalance in the optokinetic system, possibly secondary to early visual deprivation (6,7). Mustari et al., recently presented (at the International Symposium for Therapy of Ocular Motility and Related Visual Disturbances) (8) their study of the role of the pretectal nucleus of the optic tract in LN in monkey. A related theory implicates defective cortical motion processing caused by nondevelopment of binocular vision (9). Ishikawa suggested that abnormal extracorotical proprioception may predispose to LN (10). Dell’Osso et al. (11-13) postulated that LN is caused by a faulty internal representation of egocentric coordinates. The aforementioned mechanisms are not necessarily mutually exclusive; all involve various levels of visuospatial processing.

Recent data from clinical (14-18) and animal (19) studies suggest sensory abnormalities in trisomy 21 on different levels of the sensory system, both peripheral and central. These results led us to hypothesize that abnormal visuospatial processing may be responsible for nystagmus in DS, and that LN is the common form of nystagmus in DS. To test this hypothesis, we proposed to investigate the nature of nystagmus in subjects with DS, using eye movement recordings. Preliminary results have been published as an abstract (20).

METHODS

Subjects and Procedures

We examined ocular motility and visual functions in 26 unselected adults with DS (age range, 31-51 years)
LATENT NYSTAGMUS IN DOWN SYNDROME

and compared them with motility and function in an age-matched and IQ-matched group of 35 subjects with other causes of mental retardation. All subjects were recruited through local community training centers; specifically, they had not been referred to us for neuro-ophthalmologic evaluation. Clinical examination included corrected visual acuity at far and near, far fusion (Worth-four-dot test), near stereopsis (Titmus test), color vision (Ishihara plates), pupils, slit lamp and fundoscopic examinations in mydriasis, ocular motility, and alignment. Alignment was quantified at distance and near with prism bars during simultaneous alternate cover testing.

Subjects with clinically evident nystagmus and their guardians were approached regarding eye movement recording. After the subjects provided informed consent, their eye movements were recorded using the infrared technique. We also recorded the eye movements of a 3-year-old child with DS, who was referred to us because of abnormal eye movements.

Eye Movement Recording

Measurements of horizontal eye movements were made using the infrared reflection method. In the horizontal plane, the system is linear to ±20° and monotonic (single-valued) to ±25° to 30° with a sensitivity of 0.25°. The infrared signal from each eye was calibrated with the other eye covered to obtain accurate position information and document small tropia and phoria, possibly masked by the nystagmus. The child's records were uncalibrated. Eye velocities were obtained by analog differentiation of the position channels. The strip-chart recording system was rectilinear (Beckman Type R612 Dynograph, Fullerton, CA); total system bandwidth (position and velocity) was 0 to 100 Hz. Data were digitized with 12-bit resolution using a data translation board (model DT2801). The movements of both eyes were sampled at 200 Hz and stored in a computer for later analysis.

Experimental Protocol

During infrared recording, the subject was seated at the center of a 5-×-radius arc containing an array of light-emitting diodes (LEDs) subtending 0.1°. The head was stabilized in primary position using a chin cup, and the subject was instructed to move only the eyes while viewing each target as it was turned on. All recordings were carried out in a dimly illuminated room, with subjects viewing either monocularly or binocularly. The subjects did not wear their habitual correction during the experiment, because accurate fixation of LED targets does not require refractive correction. Fixation was examined by asking the subjects to view a stationary LED at 0°, alternating right eye, left eye, and binocular viewing. Saccades and effects of gaze angles were examined by asking the subjects to track horizontally stepping LEDs, at 5°, 10°, 15°, and 20° in each direction, with both eyes viewing. Smooth pursuit was examined with the subjects tracking a sinusoidal target moving at about 0.2 Hz in the horizontal plane with both eyes viewing. To evaluate the effects of near viewing, the subjects were asked to shift gaze between the far and near (15 cm) targets at 0°, both stepping and smoothly moving, while viewing with both eyes. The effects of darkness were evaluated by having the subjects fixate a stationary LED at 0° with both eyes viewing; after the lights and the LED were extinguished, the subjects were instructed to continue looking straight ahead. During the whole session, the subjects were continually encouraged to remain alert and to attend to the required task.

RESULTS

Alignment abnormalities were common in the DS group in general, with esotropia found in 16 subjects (62%), exotropia in 4 (15%), and orthotropia in the remaining 6 (23%). In contrast, most of the control subjects with other causes of mental retardation had orthotropia (70%), with exotropia in 8 (24%) and esotropia in 1 (4%).

TABLE 1. Clinical characteristics of the six adults and one child with LMLN

<table>
<thead>
<tr>
<th>Name/age</th>
<th>VA far</th>
<th>Near fusion</th>
<th>Near stereopsis</th>
<th>Alignment</th>
<th>Nystagmus</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/29</td>
<td>20/200 OU</td>
<td>Suppressed OD</td>
<td>&quot;Fly-positive&quot;</td>
<td>Eso (15 PD)</td>
<td>MLN</td>
<td>High myopia</td>
</tr>
<tr>
<td>2/4/30</td>
<td>20/50 OU</td>
<td>Present (?)</td>
<td>400 sec of arc</td>
<td>Eso (10 PD)</td>
<td>LN</td>
<td>Moderate myopia</td>
</tr>
<tr>
<td>3/m</td>
<td>20/200 OU</td>
<td>Suppressed OD</td>
<td>—</td>
<td>Eso (30 PD)</td>
<td>MLN</td>
<td>Congenital cataracts</td>
</tr>
<tr>
<td>4/3/31</td>
<td>20/100 OU</td>
<td>Suppressed OD</td>
<td>—</td>
<td>Eso (30 PD)</td>
<td>LN</td>
<td>High myopia</td>
</tr>
<tr>
<td>5/m</td>
<td>20/80 OU</td>
<td>Present</td>
<td>—</td>
<td>Eso (mild at far 20 PD at near)</td>
<td>LN</td>
<td>Hyperopia</td>
</tr>
<tr>
<td>6/m</td>
<td>20/60 OU</td>
<td>Suppressed OS</td>
<td>100 sec of arc</td>
<td>Eso (15 PD)</td>
<td>MLN</td>
<td>LE &gt; RE</td>
</tr>
<tr>
<td>7/m</td>
<td>NA</td>
<td>Suppressed OD</td>
<td>NA</td>
<td>Eso (25 PD)</td>
<td>CNV</td>
<td>Apalasia</td>
</tr>
</tbody>
</table>

Subjects 1-5 preferred to fixate with their left eye.
VA, visual acuity; PD, prism diopters; ON, optic nerve; Eso, esodeviation; OD/RE, right eye; OS/LE, left eye; OU, both eyes; NA, not available; LMLN, L, number; F, female; M, male; MLN, ML.

Far fusion was measured by the Worth-four-dot test, near stereopsis by the Titmus test.
<table>
<thead>
<tr>
<th>Subject</th>
<th>LN</th>
<th>MLN presence/direction</th>
<th>LMLN frequency (Hz)</th>
<th>LMLN amplitude (°)</th>
<th>LMLN amplitude RE vs LE</th>
<th>CN type/ frequency (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>JL &gt; JR</td>
<td>+/- left gaze</td>
<td>2-40</td>
<td>RE &gt; LE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>JL = JR</td>
<td>+/- left gaze</td>
<td>JR/JL</td>
<td>2-3</td>
<td>RE = LE</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>JL = JR</td>
<td>+/- left gaze</td>
<td>JR/JL</td>
<td>2-20</td>
<td>RE &lt; LE</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>JL &gt; JR</td>
<td>+/- left gaze</td>
<td>JR/JL</td>
<td>2-20</td>
<td>RE &lt; LE</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>JL &gt; JR</td>
<td>+/- left gaze</td>
<td>JR/JL</td>
<td>2-20</td>
<td>RE &lt; LE</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Not available for recording</td>
<td></td>
<td>NA</td>
<td>1-4</td>
<td>NA</td>
<td>Pendular/2-3</td>
</tr>
<tr>
<td>7</td>
<td>JL &gt; JR</td>
<td>+/- left gaze</td>
<td>NA</td>
<td>1-4</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 2. Nystagmus characteristics of five adults and one child with LMLN***

**Notes:**
- JL, jerk right; JR, jerk left; NA, not available; ON, central target on; OFF, central target off; RE, right eye; LE, left eye; LMLN, LN, MLN, CN.
- *For this subject, RE < LE during MLN.*
- The JR nystagmus could have been either MLN, CN with a latent component, or a mixture of the two.

Ocular motility was clinically normal in 20 of the DS subjects. We identified nystagmus clinically in six adult subjects with DS and none in the control group. Their clinical characteristics are summarized in Table 1. All showed LMLN, more prominent with one eye covered, and esodeviations from 10 to 30 prism diopters. Visual acuity ranged from 20/40 to 20/200, with near vision, J4 to J8. Stereopsis was absent or diminished (Table 1). Subjects 1 through 5 preferred their left eyes for fixation. Eye examination demonstrated mild optic nerve dysplasia in one and peripheral congenital cataracts in two. The child with DS had nystagmus with pendular and jerk components, prominent during binocular viewing.

**FIG. 1.** Example of a typical latent/manifest latent nystagmus (LMLN) recording (subject 2). While viewing with both eyes open (A), sporadic jerk-left nystagmus can be seen; it became sustained jerk-right during right-eye viewing (B) and jerk-left during left-eye viewing (C). Note the increase in the amplitude of the nystagmus while fixating monocularly (B, C) as compared with binocular viewing. The nonfixating right eye (A, C) and left eye (B) traces have been offset in position for clarity. The first and last fast phases in (B) are markedly asymmetric, a common occurrence in LMLN, in which the motion of the nonfixating, strabismic eye does not exactly mirror that of the fixating eye. Upward deflections indicate upward eye rotations. RE, right eye; LE, left eye; BE, both eyes; REN, right eye horizontal; LEN, left eye horizontal; and B, blink.
LATENT NYSTAGMUS IN DOWN SYNDROME

10 11
Time (sec)

RE Fixation

Fig. 2. Example of purely unidirectional (jerk left) latent/manifest latent nystagmus (LMLN) in subject 5, during binocular viewing (A) and left-eye viewing (C). No nystagmus is seen with right-eye viewing (B). The nonfixating right eye (A, C) and left eye (B) traces have been offset in position for clarity. Upward deflections indicate rightward eye rotations. RE, right eye; LE, left eye; BE, both eyes; REH, right eye horizontal; LEH, left eye horizontal; and B, blink.

lar viewing, and esotropia of 25 prism diopters. He was aphakic, after successful surgery for bilateral congenital cataracts. He could sustain central fixation and preferred to fixate with his left eye.

Eye movement recording was performed in five adult subjects and the child. It established the presence of LMLN with exponentially decaying waveforms in all the adult subjects with DS. We did not observe CN waveforms in any of our adult subjects. The child (subject 7) exhibited a complex combination of waveforms consisting of CN and LMLN. The CN waveforms were of both jerk and pendular varieties and also had a latent component. At times, the nystagmus was disconjugate, mimicking spasmus nutans. The ocular motor data are summarized in Table 2.

With binocular viewing, MLN was documented by the recordings to a varying degree in the five adult subjects with clinically evident nystagmus who underwent eye movement measurement. Predominant direction of the nystagmus was jerk left in all subjects. Nystagmus increased during monocular viewing and changed direction with alternating fixating eyes in four subjects (Fig. 1). In one subject, the nystagmus was unidirectional (Fig. 2), and was observed mainly while viewing with the left eye.

LMLN changed little at different gaze angles. In the adults, frequencies ranged from 2 to 5 Hz and amplitudes from 1° to 20°. When dissociated (as it was in two subjects), higher amplitude LMLN did not correlate with worse vision in that eye. Saccades were normal, but eye movements during smooth pursuit were asymmetric, reflecting the prevailing direction of the nystagmus slow phases rather than a directional asymmetry in the smooth-pursuit subsystem (21). In darkness, all subjects exhibited strong drifts in the direction of the slow phases (extended slow phase). In subjects 1, 3, and 5, attempts to fixate straight ahead without visual cues resulted in rightward shifts in the mean eye position around which nystagmus occurred (Fig. 3).

In the child (Table 2, subject 7), LMLN frequencies ranged from 1 to 4 Hz; lack of cooperation because of his age precluded accurate amplitude calibration. His CN had frequencies of 2 to 5 Hz (pendular) and 1.5 to 3 Hz (jerk and jerk with extended foveation). Examples of the child’s nystagmus are shown in Figure 4.

DISCUSSION

We found that 23% of unselected adult subjects with DS had nystagmus. In all these cases, the nystagmus was
Traditionally, latent nystagmus has been associated with nondevelopment of binocular vision (9). Yet, near stereopsis was at least to some extent preserved in two of our adults with DS and LMLN (Table 1) who showed esotropia during far viewing but esophoria while viewing near a target. Another two DS subjects, who were esotropic at near but only esophoric at far, could fuse the Worth four-dot test, suggesting the existence of hemispheric dominance in DS. That the subjects chose their left eyes for fixation, although such preference corresponded to the more prominent LN (subjects 1, 4, 5, and 7) is remarkable. This finding implies that eye dominance is determined by factors other than visual circumstances, including blindness, as previously described by Dell’Osso et al. (13) Although eye dominance and hand dominance are not directly related, three of our adult subjects were left-handed, suggesting an unusual pattern of hemispheric dominance in DS.

The presence of strabismus in LMLN is considered obligatory. Indeed, all study patients with DS had esodeviations. However, the cause of the strabismus in LMLN is unclear. Recently, extracortical proprioception has been shown to be important in the normal development of ocular alignment (24), supporting Ishikawa’s hypothesis that LN may be secondary to abnormal extracranial proprioception (10). Although no data are presently available on extracranial proprioception in DS, a plethora of evidence attests to an abnormal sensory system, on the levels of sensory nerves (18), primary sensory cortex (16), and visuospatial integration (15). Children with DS have lower conduction velocities and lower action potentials in their sensory nerves (18). Short-latency somatosensory evoked potentials in DS show prolonged interpeak latencies and abnormally large amplitudes of cortical potentials N20 and P25 in the parietal area (16). In addition to these macropotentials, potentials related to rcafferent sensory information are absent (17). Processing of proprioceptive information in DS is impaired, as reflected by kinesthetic aftereffects disrupting the spatial frame of reference (14) and poor location memory (15). Further evidence for associative cortex dysfunction in DS comes from animal models. Mice with segmental trisomy 16 (Ts65Dn mice), which serve as a model for DS, exhibit severe deficits in the integration of visual and spatial information (19).

These data suggest that impaired processing of sensory signals in DS may lead to abnormal formation of visuo-spatial maps, thus resulting in a defective internal representation of egocentric coordinates. Such abnormal internal representation of egocentric coordinates may be responsible for ocular misalignment and LMLN (both conditions being common in DS), as proposed by Dell’Osso et al. (11-13). Conversely, strabismus itself (25,26) and strabismus surgery (27,28) have been shown to affect egocentric localization. Therefore, esotropia in DS can either be caused by abnormal egocentric localization or can be directly responsible for it. Further studies are necessary to separate these two possible and interrelated mechanisms.

Evidence in support of the faulty internal representation of spatial coordinates in our adult DS subjects comes from their behavior in darkness. While attempting to fixate straight ahead in the absence of visual cues, these subjects showed rightward shifts of the mean eye position around which the LMLN oscillation occurred. Such shifts could not have resulted from switching the fixating eye, because they were not accompanied by a reversal of the LMLN direction (Table 2). Such shifts in the mean eye position were observed in addition to the drifts in the
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FIG. 4. Example of the combined congenital nystagmus (CN) and latent/manifest latent nystagmus (LMLN) waveforms in subject 7. During right-eye fixation, CN is evident, with pendular (A) and jerk with extended foveation (B) waveforms. During fixation with the left eye (C), a mixture of LN and CN waveforms is seen. *Signal saturation. Upward deflections indicate rightward eye rotations. RE, right eye; LE, left eye; BE, both eyes; REH, right eye horizontal; LEH, left eye horizontal; and B, blink.

In conclusion, frequent occurrence (23%) of LMLN in adults with DS may reflect abnormal processing of visuospatial information, consistent with recent findings in patients and animal models of trisomy 21; misalignment of the eyes and impaired binocularity also ensue. This supports the role of dysfunctional visuospatial integration in the pathogenesis of LMLN. The presence of the combination of CN and LMLN waveforms in a child with DS, but only LMLN in adults, raises the intriguing possibility of Alzheimer's disease-related changes in the waveforms.

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REFERENCES


Transient Vertical Diplopia and Silent Sinus Disorder

François-Xavier Borruat, MD, Bertrand Jaques, MD, and Jacques Durig, MD

A 57-year-old man had isolated transient recurrent vertical diplopia. Left hypoglobus and enophthalmos were present. Investigations revealed an otherwise asymptomatic left maxillary chronic aspecific sinusitis, with 8 mm lowering of the left orbital floor. Transient diplopia was thought to be secondary to transient fusion impairment. Orbital floor reconstruction cured the patient.

Key Words: Transient diplopia—Silent sinus syndrome.

Transient diplopia is not a frequent complaint and etiologies include myasthenia, dysthyroidism, multiple sclerosis, decompensation of a preexisting phoria, dorsal mesencephalic syndrome, ocular neuromyotonia, and giant cell arteritis. Sinus disorders can involve the orbit and produce proptosis, enophthalmos, diplopia, pain, or visual loss. However, in most cases the clinical presentation is typical enough to suggest the sinus origin.

We report an unusual case of a patient who complained of isolated transient vertical diplopia as the sole symptom of an underlying otherwise silent sinus disorder.

**CASE REPORT**

In April 1994, a healthy 57-year-old man complained for the first time of isolated vertical diplopia while driving his car. The episode lasted a few minutes, resolving spontaneously. Despite disappearance of symptoms, ophthalmologic examination revealed vertical ocular dissociation diagnosed as right trochlear palsy. With prisms, evolution was stationary until May 1994 when transient vertical diplopia recurred. Magnetic resonance imaging (MRI) was performed with angiography sequences. Neither brain nor brainstem lesions was found. Left maxillary sinus was homogeneously filled, but this finding was not considered.

A neurologist diagnosed an isolated left inferior oblique palsy. In November 1994, because of persistent and fluctuating vertical diplopia, the patient was examined by another ophthalmologist who diagnosed paresis of the left superior rectus and inferior oblique muscles with a comitant deviation and exyclotorsion of the left eye. Myasthenia was suspected but excluded by neurologic examination. The neurologist noted a slight increase in vertical deviation and concluded to a probable decompensation of a preexisting vertical phoria.

The patient was referred for neuro-ophthalmologic examination in December 1994. Visual function was normal in both eyes (visual acuity 20/20 in both eyes, Ishihara color plates 13/13 OD, visual fields full to confrontation), and slit lamp and fundus examination were normal in both eyes. Intraocular pressure was 16 mmHg in the right eye and 14 mmHg in the left eye. A slight asymmetry of the patient's face was noticeable with a narrowed left palpebral fissure (10 mm right side, 9 mm left side), a lower positioned left eye, and 2 mm of left enophthalmos (Fig. 1). Oculomotoric examination showed a right variable hypertropia; smooth pursuit and saccades were normal. Trigeminal and facial nerve examination was normal. A CT scan was performed, showing the left maxillary sinus to be homogeneously filled and 8 mm of inferior displacement of the left orbital floor, which was markedly thinned (Fig. 2). On repeat questioning the patient recalled that sinus surgery was performed twice in 1957.

An ears, nose, and throat examination and left maxillary sinus exploration was performed. The left maxillary sinus was lined by polypoid mucosa and filled with thick mucoid material, without bacteria, fungi, or malignant cells. The pathologic diagnosis was chronic nonspecific sinusitis. Two months later, orbital floor reconstruction was performed and the patient has since been asymptomatic.

**COMMENT**

Over the course of 37 years, our patient developed a chronic asymptomatic sinusitis that resulted in progressive thinning of the orbital floor, which was fully preserved. Thus, enophthalmos and hypoglobus were not related to orbital floor disruption, but were caused by an inferior displacement of the orbital content probably secondary to a contraction of the sinus cavity.
Silent sinus syndrome is a rare disorder resulting in spontaneous enophthalmos and hypoglobus (1). Lowering of the orbital floor occurs secondary to asymptomatic maxillary sinus disease with secondary thinning of the bony orbital floor. Most of the cases reported by Soparkar et al. (1) presented mild to moderate hypoplasia of the ipsilateral maxillary sinus. From their retrospective multicentric study, they collected 14 cases but none with diplopia. Five other patients have been reported in the literature, also none with diplopia (2-5). All these patients were diagnosed secondary to the development of enophthalmos and hypoglobus, none complaining of diplopia.

Our patient complained of transient vertical diplopia in association with a silent sinus disease. He was the oldest of all published similar cases (average age, 37 years; range, 29-46 years) (1) and his amount of hypoglobus (8 mm) was the highest (average, 3.4 mm; range, 2-6 mm) (1). Evolution was slow, spanning over 37 years. Most likely, transient vertical diplopia was caused by progressive inability to compensate for 8 mm of hypoglobia. Silent sinus syndrome should be kept in mind.
as a diagnostic possibility in patients with fluctuating transient vertical diplopia.

REFERENCES


Posterior Optic Nerve Infarction After Lower Lid Blepharoplasty

Catriona D. Good, Lorraine M. Cassidy, Ivan F. Moseley, and Michael D. Sanders

We describe a case of acute and total loss of vision after lower lid blepharoplasty. This major complication followed minor cosmetic surgery. Magnetic resonance imaging (MRI) showed posterior segmental infarction of the optic nerve, a finding not previously demonstrated.

Key Words: Blepharoplasty—Blood supply—Complication—Optic nerve—Optic nerve infarction—Visual loss.

CASE REPORT

A 68-year-old woman had carbon dioxide laser therapy and lower lid blepharoplasty for bags under her eyes and wrinkles. The surgery was carried out under local anesthetic and sedation as a day case. Transconjunctival injections of Lignocaine 2% (International Medication Systems (UK) Ltd, Surrey, England) with adrenaline were performed bilaterally. Incisions were made through the conjunctiva into the fat bags using a CO₂ laser. Haemostasis of large blood vessels was secured with diathermy, the fat was excised, and the lower lids allowed to return to their natural position. Afterwards, periorcular resurfacing of wrinkles was performed using the FeatherTouch technique.

Immediately after the procedure there was slight oozing of blood from the left lower lid margin, which settled, and the patient was discharged 2 hours later. Later that night she had marked swelling and bruising around both eyes and was unable to open her right eye. The next day she experienced rapid, complete visual loss from the right eye, which had been normal preoperatively. Examination revealed marked bilateral periorbital swelling and subconjunctival haemorrhages more marked on the right (Fig. 1). In the right eye, there was no light perception and the pupil was fixed and semidilated. The left eye acuity was 6/6 and ocular examination was normal.

Magnetic resonance imaging (MRI) performed 5 days after surgery showed mixed signal in the right lower lid on T1-weighted images, compatible with the known hemorrhage (Fig. 2A). There was no major haematoma in the right orbit, but there were two small pockets of hemorrhage in the retrobulbar fat on the right side and the fat appeared diffusely swollen and inhomogeneous, suggesting diffuse oedema or congestion (Figs. 2B and C). There was no proptosis and the optic nerve was not displaced. The axial T2-weighted images (Fig. 3A) showed clearly defined high signal in a segment of the optic nerve starting 13 mm behind the eye and extending posteriorly for 7 mm. The anterior and posterior margins were orthogonal to the long axis of the nerve. Coronal images (Fig. 3B) confirmed that the full thickness of the nerve was involved. The remainder of the anterior optic pathway appeared completely normal. Contrast medium was not given.

DISCUSSION

Visual loss is a rare but well-documented complication of blepharoplasty (1), although previous reports have not documented MRI changes within the optic nerve localizing the site of damage.

In a national survey of 3,000 ophthalmologists in the United States performing blepharoplasties (98,514,000 lid procedures), the frequency of blindness as a complication was found to be 0.04% (2).

Visual loss after blepharoplasty is well described in the literature, but the mechanism has not been elucidated. The most likely factor is increased intraorbital pressure and vascular compromise consequent on hemorrhage or oedema within the orbit induced by operative manipulation (3). During the operation, the fat is removed from the orbit and blood can ooze from the cut surface of the fat. The hemorrhage may be venous or more likely arteriolar and may depend on the fascicular arrangement of the orbital compartments. Pockets of blood, oedema, and air may be trapped within the fascial planes, elevating the orbital pressure so that perfusion of the pial network around the optic nerve is impaired. Therefore, MRI may show only a modest amount of blood within the orbit. Hemorrhage may also spread along the periosteum toward the back of the orbit and compress the optic nerve in the orbital apex, although we saw no evidence of this in our case.

Alternative mechanisms for visual loss have been suggested and these include compromise of the central reti-
nal artery (4–6) or vein (7) with ischemia of the anterior optic nerve or acute angle-closure glaucoma in susceptible individuals (3). The critical duration of impaired perfusion needed to cause permanent blindness varies and depends on the degree of orbital hemorrhage and the rapidity and degree of increased intraorbital pressure, but probably ranges from 1 to 4 hours. Some recovery can be expected if reperfusion occurs within 1 to 1.5 hours (6). The visual morbidity can be minimized with early diagnosis and surgery to open up the fascial layers (8). Hislop et al. proposed a protocol for the management of patients with retrobulbar hemorrhage in an attempt to reduce the incidence of blindness (5). In 1988, a technique was introduced for upper and lower lid blepharoplasty that combined the advantages of a transconjunctival approach and CO₂ laser as the only cutting tool (9). This was aimed at reducing complications attributable to hemorrhage; however, removal of orbital fat is an essential part of the surgery and results in hemorrhage irrespective of the incisional instrument.

In our case, there was infarction of the posterior portion of the intraorbital optic nerve with sparing of the anterior and intracanalicular portions. MRI demonstrated two tiny pockets of hemorrhage within the retrobulbar fat and diffuse edema in the right orbit (Figs. 2A–C). The clearly defined area of increased signal within the right optic nerve on the axial T2-weighted images was situated behind the entrance of the central retinal artery, which pierces the dura 12 mm behind the optic disc. This portion of the nerve is supplied by peripheral centripetal arteries of the pial plexus with no axial centrifugal system except for a short recurrent branch extending back from the central retinal artery for 2 to 3 mm in approximately 20% of the population (10). This contrasts with the anterior optic nerve, which receives a centrifugal supply from the central retinal artery and a centripetal supply from the pial plexus. The intracanalicular portion is supplied by separate branches of the ophthalmic artery, which form semicircles on the upper and lower surfaces of the optic nerve. The pial supply is relatively deficient within the optic canal (10).

In our case, there was marked subconjunctival hemorrhage with only small pockets of blood in the retrobulbar fat, but this was associated with marked edema or congestion of the infraorbital fat. We suggest that this caused increased intraorbital pressure and compromise of the centripetal pial plexus with consequent infarction of the posterior portion of the intraorbital optic nerve. The anterior and canalicular portions of the optic nerve, with alternative blood supplies, were not compromised. Unfortunately immediate attempts to decompress the optic nerve were not made in this case.

Despite the newer surgical techniques that are designed to prevent retrobulbar hemorrhage, blindness is
FIG. 2. A: Coronal T1-weighted (400/10) magnetic resonance image demonstrating high signal subacute hemorrhage in the right lower lid. B: Coronal fast spin echo T2-weighted (3000/102) image with fat saturation, showing increased signal in the edematous, swollen retro orbital fat within the right orbit with normal signal return from both anterior optic nerves. C: Axial T1-weighted (400/10) image with fat saturation, showing two small pockets of hyperintense hemorrhage within the intermediate signal of the edematous orbital fat.
still a risk after blepharoplasty and patients need to be carefully monitored in the postoperative period to detect critical increased intraorbital pressure.

REFERENCES
Optic Disc Edema in Neonatal Onset Multisystem Inflammatory Disease (NOMID)

Andrew G. Lee, MD, and Robert W. Warren, MD

Purpose: To inform ophthalmologists about neonatal onset multisystem inflammatory disease (NOMID), a rare condition with ophthalmologic manifestations.

Methods: We report a single case of NOMID with optic disc edema.

Results: A 28-month-old child with neonatal rash, arthropathy, central nervous system (CNS) involvement, and optic disc edema was diagnosed with NOMID.

Conclusions: The finding of posterior uveitis or optic disc edema in a child with juvenile onset arthritis may allow the differentiation of NOMID from juvenile rheumatoid arthritis.

Key Words: Neonatal onset multisystem inflammatory disease.

Neonatal onset multisystem inflammatory disease (NOMID) is a rare systemic inflammatory disease of unknown etiology and pathogenesis characterized by the triad of neonatal rash, arthropathy, and central nervous system (CNS) involvement. Although ocular involvement has been reported previously in the pediatric and rheumatologic literature, to our knowledge this is the first reference to the neuro-ophthalmologic findings of NOMID in the English language ophthalmic literature (1–3).

Case report

A 28-month-old white boy was referred for evaluation of optic disc edema. He was a 7 pound and 2 ounce 39-week gestational product of an uncomplicated pregnancy and vaginal delivery on March 27, 1996. At birth, the infant was noted to have a generalized urticarial rash. The rash thereafter varied in intensity, but was present nearly continuously. His developmental history included sitting up at age 4 months, but he did not crawl until late April 1997 (age 13 months). His length was in the 50th percentile at 7 months but dropped to the 25th percentile and then the 10th percentile over the next year. His weight remained stable at the 80th percentile.

In February 1997, he developed difficulty with his right lower extremity. Physical examination demonstrated external rotation of the right leg and radiographs revealed closure of the epiphyseal growth plate.

Laboratory evaluation revealed hemoglobin of 9.3 g/dl (normal 11.5 g/dl) and a white blood cell count of 22,000/mm³. Erythrocyte sedimentation rate measured 35 mm/h. He had intermittent, recurrent fevers up to 103°F. Multiple skin biopsies of the recurrent rash were consistent with chronic urticaria. The patient developed generalized, diffuse, non-tender lymphadenopathy and moderate hepatomegaly. An inguinal lymph node biopsy showed no evidence of malignancy. Bone marrow biopsy was unremarkable. The patient had arthralgias and pain in the right knee. He was seen by rheumatology on May 16, 1997. His weight was 10.9 kg (60th percentile) and his height was 74.1 cm (7th percentile). Neurologic examination revealed mild gross motor delay. The diagnosis of NOMID was made and the patient was treated with oral nonsteroidal agents.

Ophthalmologic examination in June 1997 revealed a visual acuity of fixing and following in each eye. There was no nystagmus. The pupils were equal in size with a normal light reaction in each eye and no afferent pupillary defect. There was no evidence of anterior segment inflammation. Motility examination was full. Visual fields were not tested formally. Tactile tonometry was normal. Ophthalmoscopy revealed bilateral optic disc edema. There was no evidence of posterior uveitis.

A computed tomography (CT) scan of the head was normal on May 28, 1997 and there was no hydrocephalus. The patient had chronic inflammatory aseptic meningitis, and lumbar puncture on May 29, 1997 revealed 250 white blood cells/mm³ (56% polymorphonuclear cells and 42% mononuclear cells). The cerebrospinal fluid (CSF) protein was 33 mg/dl (normal = 15 to 45 mg/dl), and CSF glucose was 42 mg/dl. CSF gram stain and cultures did not demonstrate any organism. Repeat CSF studies on July 17, 1997, revealed 80 white blood
cells/mm³ (70% polymorphonuclear cells) and repeat CSF on May 28, 1998, revealed 170 white blood cells/mm³. The patient was treated with oral corticosteroids and had improvement in the optic disc edema. He experienced exacerbations and remissions of his systemic symptoms and recurrent optic disc edema and was treated with pulse intravenous corticosteroids and methotrexate. He had marked improvement in his optic disc edema on this treatment regimen. In July 1998, he had mild optic atrophy in the right eye and mild hyperemia of the left optic disc but no uveitis or optic disc edema.

**DISCUSSION**

NOMID is a rare multisystem inflammatory disorder that may have ocular and CNS involvement. The characteristic features were summarized from 32 cases in the literature by Torbiak et al. (1). These include the following: 1) a severe, asymmetric, deforming, painful arthropathy usually affecting large joints (100%) with almost pathognomonic bizarre epiphyseal radiographic changes (80%); 2) a generalized, evanescent macular or maculopapular rash with urticarial features (100%); 3) failure to thrive (100%); 4) recurrent or persistent fever (100%); 5) generalized adenopathy or hepatosplenomegaly (100%); and 6) CNS involvement such as chronic meningitis with CSF pleocytosis (88%), intellectual impairment (87%), seizures (33%), and sensorineural hearing loss (22%) (1). The hematologic abnormalities include anemia (100%), increased erythrocyte sedimentation rate (100%), increased complement levels (60%), increased immunoglobulins (75%), and persistent leukocytosis (100%). Rheumatoid factor was positive in only 6% and no patients had a positive antinuclear antibody (1).

The ocular manifestations of NOMID include uveitis and optic disc edema (1–3). Prieur and Griscelli reported three patients with NOMID (2). Of these three patients, all had optic disc edema, one had a paralimbic keratitis of the inferior hemicornea, and one had conjunctivitis and posterior synechiae (2). Yarom et al. reported anterior and posterior uveitis as well as optic disc edema in two patients with NOMID (3). Torbiak et al., in their review of the literature in 1989, reported ocular inflammation in 12 of 14 patients (86%), and hydrocephalus was reported in 14 of 15 patients (93%) (1).

The pathogenesis of the optic disc edema in NOMID may be an inflammatory optic neuritis related to the primary multisystem inflammation and posterior uveitis, an infiltrative optic neuropathy caused by the chronic meningitis, or most likely, optic disc edema caused by increased intracranial pressure.

The pathogenesis of NOMID is poorly defined. Intrathecal or intrapartum infection or abnormal regulation of the inflammatory response have been implicated in NOMID. Despite extensive evaluations, a precise infectious or inflammatory etiology has not been identified. The treatment of NOMID remains unclear, but nonsteroidal antiinflammatory drugs, steroid, and other immunosuppressive agents have been used with some success (1–3).

The primary differential diagnosis is systemic onset juvenile rheumatoid arthritis (JRA). CNS involvement and optic disc edema, although common in NOMID, are uncommon in JRA. Anterior uveitis, although reported in JRA (particularly the pauciarticular form in girls), is rarely present in systemic JRA and posterior uveitis is even more uncommon in JRA (1–3). Thus, documentation of posterior uveitis and optic disc edema may allow differentiation of JRA from NOMID. Although NOMID and JRA share similar clinical profiles, NOMID has distinguishing features including onset during the first few days of life, persistent symptoms, arthropathy with more joint deformity and bony prominence, absence of morning stiffness, and distinctive radiographic findings (e.g., enlarged epiphyses and patellar overgrowth) (4).

**REFERENCES**

Idiopathic Intracranial Hypertension
A Case Report With Optic Nerve Histopathology

Hilary C. Horgan, Robert M. McFadzean, and William R. Lee

We present the clinical and pathologic findings in an atypical case of idiopathic intracranial hypertension. A 51-year-old man had headaches, visual deterioration, papilledema, and deafness. Neuroimaging was normal, and cerebrospinal fluid pressure monitoring confirmed increased intracranial pressure. The patient was treated with a ventriculo-peritoneal shunt. Histopathology revealed grossly atrophic optic nerves with almost complete axonal loss. The prelaminar portion of the optic nerves was thickened by gliosis and hyalinized capillaries, which have not been described previously.

**Key Words:** Idiopathic intracranial hypertension—Visual loss—Ventriculo-peritoneal shunt—Axonal loss.

Idiopathic intracranial hypertension (IIH) is a disease primarily of obese women in their second to fourth decades of life (1). It is characterized by increased intracranial pressure, without evidence of an intracranial mass, enlargement of the ventricles, or abnormal composition of the cerebrospinal fluid (CSF). The most significant complication of IIH is permanent visual loss caused by prolonged papilledema with secondary optic atrophy. Visual impairment is demonstrable in up to 90% of patients, but most of these have only minor defects (2). The cause is unknown, and because the disorder is not life threatening, there is little histopathologic data available. One previous paper reports severe optic atrophy with 80% to 90% axonal dropout that was more marked in the peripheral area of each optic nerve (3,4). We report the histopathologic findings in the optic nerves in an atypical case of IIH.

**CASE SUMMARY**

A 51-year-old man was referred for investigation of headaches, deafness, and deteriorating vision. He gave a 2- to 3-year history of throbbing, frontal headaches that were worse on awakening. His vision had deteriorated gradually in his right eye during the previous year. His hearing impairment was initially episodic but recently had become constant.

On examination, best corrected Snellen visual acuity for right eye was CF and left eye 6/9. There was a right relative afferent papillary defect. Ocular motility was normal. The right visual field to confrontation showed a large centro-circinal scotoma and generalized constriction. The left Bjerrum central visual field showed enlargement of the blind spot and generalized peripheral constriction with a 3-mm white target. Dilated fundoscopy showed moderate bilateral papilledema with developing pallor of the right optic disc.

Full blood count, erythrocyte sedimentation rate, urea, and electrolytes were normal. A computerized tomography (CT) scan enhanced with contrast was normal and audiologic investigations revealed a bilateral, degenerative sensorineural deafness. A lumbar puncture showed clear CSF, under high pressure with <5 nucleated cells/mm³, protein 0.35 g/L, and glucose 6.3 mmol/L. No organisms were grown on culture. The patient unfortunately defaulted from follow-up and did not return to the clinic for 8 months when his corrected Snellen visual acuity had deteriorated further to right eye: no perception of light, and left eye: 6/24. A relative afferent papillary defect was present on the right. Both optic discs were diffusely atrophic (more marked in the right eye), and the left visual field had become reduced to a small temporal island. Another CT scan and bilateral carotid angiography showed no abnormality, in particular no evidence of a venous sinus occlusion. Intracranial pressure monitoring was performed using an indwelling ventricular catheter and confirmed persistent elevation of the mean intracranial pressure higher than 35 mm Hg. The CSF had <5 nucleated cells/mm³, with normal protein and glucose. No organisms were grown on culture.

A diagnosis of atypical IIH was made and the patient was commenced on 4 mg dexamethasone 6 hourly. Unfortunately, he developed glycosuria and a fasting blood glucose confirmed diabetes mellitus. A ventriculo-peritoneal (V-P) shunt was inserted and his headaches settled. Postoperatively, his visual acuity and fields remained unchanged.
Nineteen months later, his headaches returned because of blockage of the V-P shunt, and a revision was carried out. Thereafter, the patient was followed up for another 10 years, during which time his visual acuity and fields were unchanged. A plain CT tomoscan carried out at final follow-up showed normal-sized ventricles with effective drainage by the shunt.

Unfortunately, the patient died suddenly, 11 years after presentation. At autopsy, the cause of death was found to be myocardial infarction.

**PATHOLOGY**

The globes were removed at autopsy within 24 hours of death and fixed in 2% buffered glutaraldehyde before paraffin embedding. Macroscopic examination of both eyes revealed normal dimensions 24 x 23 x 23 mm. The attached optic nerve and surrounding sheath in each specimen measured 15 mm in length and 8 mm in diameter. On section, both optic nerves were atrophic (3 mm diameter) and the dilated subarachnoid space was filled with loose fine white tissue strands (Fig. 1). On the nasal side, the subarachnoid space appeared more distended (3 mm in horizontal alignment) than on the temporal side, where the dura was more in line with the edge of the scleral canal (Fig. 2). The prelaminar part of the optic discs were atrophic and projected forward.

Microscopic examination revealed a normal anterior segment, lens, and vitreous in each eye. Serial sections (10 μm) were taken from the blocks and optic nerves and stained with conventional stains: Haematoxylin and Eosin (H&E), Periodic acid Schiff (PAS), Prussian Blue, Loyez, and Bodian. The following immunohistochemical reactions were applied: S100, neuronal specific enolase (NSE), and neurofilaments. Apart from the peripapillary retina (see later), the retinal photoreceptor layer, the retinal pigment epithelium, and the choroid were normal. Throughout the retina the ganglion cell layer was atrophic and this change was most pronounced at the fovea. It was possible to identify a few surviving axons in the nerve fiber layer of the retina in each eye using immunohistochemistry. In both eyes, the prelaminar part of the optic nerve was thickened by glial tissue that contained numerous hyalinized capillaries (Fig. 3). The peripapillary retina was atrophic and the photoreceptor layer was replaced by glial cells. This was accompanied by patchy atrophy of the retinal pigment epithelium and choroidal fibrosis, although the choroidal vessels were patent (Fig. 4). Horizontal longitudinal sections through the optic nerves of both eyes revealed atrophy that was more extensive on the temporal side (Fig. 5). Axons were identified within the atrophic nerve bundles on the nasal side in the left eye but were not identified with certainty in the right eye. In transverse sections through the optic nerves, myelinated axons were identified on the nasal side of the axial part of the left optic nerve but were unidentified in the right optic nerve. The trabeculae in the subarachnoid space were of normal thickness.

**NEUROPATHOLOGIC FINDINGS**

On gross examination the fixed brain weighed 1,480 grams. There was no evidence of tentorial or tonsillar...
A defect in the lateral aspect of the right parietal lobe was seen through which the V-P shunt protruded. The ventricles were of normal size. The occipital cortex appeared normal.

Histologic examination showed a thickened dura along the convexity with collections of chronic inflammatory cells in a relatively acellular collagen matrix. The sagittal sinus showed features of longstanding occlusion with partial recanalization and the occlusion appeared organized with collections of chronic inflammatory cells. The appearances were those of pachymeningitis, which presumably was the cause of the longstanding occlusion of the sagittal sinus, but the cause of this pachymeningitis was unclear. The V-P catheter tip was blocked by ingrowth of glial cells and capillaries, cuffed by lymphocytes. The neuropathologic examination was carried out by Professor D. L. Graham and Dr. J. A. R. Nicoll.

**DISCUSSION**

We report the histopathologic changes in the optic nerves in an atypical patient with IIH. Although the patient had features typical of IIH (headaches, papilledema, visual field loss, and increased intracranial pressure), his age and sex were atypical of this condition. Substantial visual deterioration is also unusual in IIH.
According to one author (5), only 10% of IIH patients develop bilateral severe permanent visual loss. Progressive sensorineural deafness is not a feature of IIH, although tinnitus is common. This patient had diabetes mellitus but no evidence of hypertension or renal impairment, which are sometimes associated with IIH (6). There were no other neurologic signs apart from deafness, despite the unusual neuropathologic findings at postmortem. No previous imaging studies, including contrast-enhanced CT scanning and carotid angiography, had suggested a sagittal sinus thrombosis.

The patient was seen 7 months before his death when his visual acuities and fields remained unchanged, with no recurrence of headaches. It was unusual to find blockage of the ventricular-peritoneal shunt at postmortem, in the absence of signs and symptoms of increased intracranial pressure before his death. Possibly, the initial pathology was the sagittal sinus thrombosis with a secondary increase in intracranial pressure. However, bilateral carotid angiography carried out at the time of presentation did not show any evidence of thrombosis. His symptoms settled with insertion of a V-P shunt, which at a later stage, became blocked without any subsequent increase in intracranial pressure because of recanalization of the sagittal sinus demonstrated at autopsy. Thus, it appears that the sagittal sinus thrombosis was a secondary event, which subsequently resolved spontaneously.

The presence of numerous hyalinized capillaries in the prelaminar part of the optic nerve is difficult to explain. Endothelial proliferation of the capillaries and smaller vessels has been previously described along with proliferation of neuroglia in longstanding papilloedema (7,8). The most plausible explanation is that there was capillary dilation when the disc was oedematous. If there was endothelial ischemia at this stage, the integrity of the capillary monolayer may have been compromised, resulting in plasma leakage and multilayering of the basement membrane with endothelial repopulation. Contraction of the glial cells could possibly have accentuated the number of capillaries to give a false impression of previous proliferation of vessels within the nerve head. Nonetheless, reactionary neovascularization cannot be totally discounted.

This case highlights the dilated subarachnoid space around the optic nerve, which is more marked on the nasal than the temporal side (Fig. 2). In a healthy eye, the subarachnoid space is widest anteriorly and with a temporally directed scleral canal wider on the nasal side than the temporal side (9). This finding is interesting because the temporal side (9). This finding is interesting because most optic nerve sheath decompression procedures are performed with a medial approach, which is easier to perform and has fewer potential complications (10). In addition, decompression of the more dilated, medial subarachnoid space may create a better fistula leading to more rapid and complete resolution of papilloedema.

Only one other pathologic study of IIH has been reported in the literature (3,6). Our findings of significant axonal loss in the periphery of the left optic nerve are in keeping with this previous report. The few remaining axons that were seen in the left eye corresponded well with the patient's remaining small temporal field of vision in that eye. The myelinated axons were only seen in the axial and nasal areas of the left optic nerve, with almost total loss of axons in the more peripheral parts of the nerve. The right eye had no identifiable myelinated axons correlating with no perception of light in this eye. It appears that the most central nerve fibers were the most protected from the effects of increased intracranial pressure (4). These small centrally placed axons are less subject to mechanical forces and ischemia than more peripherally placed axons. Perhaps the greater distortion of the nasal than the temporal subarachnoid space protects the nasal optic nerve axons and temporal visual field from the extreme effects of increased intracranial pressure.

REFERENCES
Functional Magnetic Resonance Imaging in the Visual System

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Functional magnetic resonance imaging (fMRI) is a relatively new technique for measuring brain function during resting and activated conditions with good spatial and temporal resolution. Because of a robust and reproducible activation response to visual stimuli in the occipital cortex, many studies have been directed at visual function. The methodology has been refined progressively to allow more accurate detection of the small activation signal, and using computational mapping tools of cerebral activity have been displayed in a two-dimensional format. Several factors modifying the activation signal have been identified.

fMRI has been used to define the retinotopic representation of retinal boundaries and the localization of higher visual functions in the occipital cortex. Motion perception in area middle temporal (MT) is well-recognized, but eye movement studies are limited.

The activated signal may have significant implications for our understanding of brain metabolism, but cerebral blood flow and oxygenation sensitive recordings after prolonged visual stimulation have given conflicting results. Clinically, fMRI can follow changes in cerebral activity during a progressive neurological illness and measure responses to treatment. Neurosurgical planning in disorders such as epilepsy may be facilitated.

Key Words: Functional magnetic resonance imaging — Vision.

There are several techniques available for measuring brain function during resting and activated conditions, including direct cortical electrical stimulation, scalp recorded electrical evoked potentials, single photon emission computed tomography (SPECT), positron emission tomography (PET), magnetoencephalography (MEG), near-infrared spectroscopy (NIRS), magnetic resonance spectroscopy (MRS), and functional magnetic resonance imaging (fMRI). Because these techniques depend on different principles, the resultant brain mapping may reflect different neuronal activation processes. In addition, these techniques have different temporal and spatial resolution properties.

Direct electrical stimulation of the cortical surface depends on activation or disruption of local cortical circuits with a spatial resolution of 5 to 10 mm and a temporal resolution of a few seconds. Visually evoked potentials and MEG probably reflect underlying neuronal activity but have poor spatial resolution, although excellent temporal resolution of milliseconds. SPECT uses (99mTc) HMPAO as a cerebral blood flow (CBF) imaging agent with a spatial resolution of 8 to 9 mm and a temporal resolution of approximately 45 seconds. PET using H2 15O tracer measures changes in local CBF after neuronal activation. Its spatial resolution is 4 to 5 mm, but its temporal resolution is governed by the time required for clearance of the tracer from the bloodstream, about 50 seconds. Optical imaging with near-infrared photons combines good temporal resolution with spatial resolution of at least 5 mm. MRS provides a useful measure of regional brain chemistry but with poor spatial (1,000 mm2 at best) and temporal resolution. The relatively recent introduction of fMRI (1-6) permits activation mapping of the brain in a noninvasive manner with a potential spatial resolution of <1 mm (7) and temporal resolution of <1 second (8, 9) using fast MR or echo-planar imaging (EPI) techniques (10-12). fMRI is thought to measure local changes in blood oxygenation after increases in CBF and modification of oxygen utilization after neuronal activation (vide infra) (1,5,6,13). The presence of a robust activation response to visually evoked stimuli in the occipital cortex has made the striate and extra-striate region a particularly attractive area to study. In addition, the gatekeeper role of the primary striate visual cortex (area V1) in the determination of higher visual function is well-known, whereas the local anatomy and boundaries of the striate cortex have been studied extensively and are well-understood. The technique is useful not only in the mapping of localized cerebral cortical functions in normal individuals, but also in the assessment of disease processes (14,15) and monitoring of psychiatric disorders (16,17) and psychopharmacologic treatments (18). A typical activation pattern in the occipital cortex on exposure to an alternating black and white checkerboard is shown in Figure 1.

The advantages of fMRI are considerable in that the technique allows noninvasive imaging with excellent...
fMRI IN THE VISUAL SYSTEM

Spatial resolution almost in real time. Thus, it is possible to carry out repetitive studies on normal subjects with reasonable reproducibility and to follow changes in cerebral activity during the course of a progressive disease, including assessment of recovery patterns and responses to treatment in various neurologic disorders such as stroke and head injury. Dyslexia and albinism (19,20) can be evaluated and neurosurgical planning facilitated (21-23). This is in contrast to radionuclide techniques such as PET and SPECT, in which repeated studies are constrained by ethical considerations and radiation dosage. Advanced technology with fast scanning times and multislice cerebral images makes it possible to scan the entire brain within a short time scale and identify regions of interest (ROI) activated by different experimental paradigms. Furthermore, appropriate scanning facilities are widely available in neuroscience departments. Unfortunately, as with conventional MRI, individuals with cardiac pacemakers or retained foreign metallic material in their body must be excluded and claustrophobic patients find the technique difficult to tolerate. Volunteer or patient cooperation is crucial not only for participation in the activation task, but also in the maintenance of immobility during the scanning period to avoid misregistration artifacts (24,25). However, image processing algorithms are available that can overcome the effects of patient movement to some extent by realigning the images (26). Cerebral tissue close to the air-filled sinuses (e.g. at the base of the brain) is prone to signal void artifacts, but this is not a problem with studies of the visual cortex. While images can be acquired in close to real time, fMRI in common with PET and SPECT scanning has the disadvantage of measuring alterations in CBF that change over a period of seconds compared to the millisecond time scales of the initiating neuronal event. It is unlikely that fMRI will ever be able to investigate events with such a short time scale, which require instead the high temporal resolution of EEG or MEG.

PRINCIPLES OF METHOD—THE BOLD EFFECT

Initial activation studies in the primary visual cortex were based on images of cerebral blood volume after injection of a bolus of paramagnetic contrast agent, such as gadolinium diethylene triamine penta-acetic acid intravenously, obtained before and during stimulation with a flashing light (2). Cerebral blood volume increased during visual stimulation, but this technique required the use of an external contrast agent. Based on the magnetic properties of hemoglobin and their effect on the magnetic resonance (27,28), it was realized that paramagnetic deoxyhemoglobin could be detected in contrast to diamagnetic oxyhemoglobin and therefore used as an endogenous contrast agent (29). This difference in the physical properties of hemoglobin means that when blood flows through cerebral tissue deoxyhemoglobin creates point magnetic inhomogeneities within blood vessels, which result in microscopic field distortions around those vessels. As the coherence of the signal from hydrogen nuclei in water in surrounding tissue is partially destroyed by these microscopic inhomogeneities, the signal intensity during MRI is lower than it would be if they did not exist. During neuronal activation, a substantial increase in the metabolic demand of the local cerebral tissue involved results in a corresponding increase in CBF and oxygenation, which more than compensates for that demand (30,31). Consequently, there is a decrease in the local concentration of deoxyhemoglobin resulting in an increase in the intensity of the local MR signal. This finding has enabled the use of MRI in the monitoring of local modulations in the level of blood oxygenation associated with brain activity (32).

The activated signal in the cerebral cortex is referred to as the blood oxygenation level dependent (BOLD) contrast effect. The size of the signal is relatively small (range 2-10%); therefore, optimization of the visual stimulus and recording conditions is important. Its precise origin has not been identified, but it is believed to arise from around small venules in the cerebral cortex (33,34). The signal intensity can be correlated with local changes in CBF, tissue oxygenation, and neural activity (5,35). Typically, activity is averaged during a time scale of 2 to 6 seconds and the volume of each individual image element is 1 to 27 mm³ of cerebral cortex (36). During recordings, particular attention must be paid to avoidance of artifacts because of volunteer or patient movement (e.g. head movement, eye movements, and physiologic changes such as the cardiac pulse and respiration). Considerable concern has been expressed that subject movement during activation may correlate with the task being performed and the resulting signal changes be mistaken for evidence of brain activation, e.g., flinch.
ing when a flashing light comes on or goes off (37,38). An assessment of the effect of stimulus-correlated motion using conventional visual and motor protocols and an image coregistration technique showed stimulus-correlated motion and synthetic cumulative difference images with a striking similarity to the equivalent functional image in each case (37). Even objects moving outside the field of view may have an effect on the fMRI signal if temporally correlated with the performance of a particular task (39). However, these artificial signal intensity changes were characterized by their location, greater magnitude, and more rapid increase to a maximum than those seen from typical activations (25). The increasing recognition of false-positive signals has stimulated efforts to develop a robust processing technique with clearly defined failure modes. Improved functional activation maps have been obtained using navigator echoes to monitor and compensate for signal fluctuations caused by motion, while, by simultaneously monitoring the respiration and heartbeat during the acquisition of imaging data and retrospectively synchronizing the imaging data with physiologic activity, physiologic effects have been estimated and removed (24).

Variations in venous deoxyhemoglobin levels in response to neuronal activation represent a complex interplay between focal changes in CBF, cerebral blood volume, and regional metabolism. Various mathematical models attempt to categorize the response of venous oxygenation to changes in these variables to obtain a quantitative understanding of changes in blood oxygenation and to relate these changes to the observed dynamics of the fMRI signal change (13,35,40).

METHODOLOGY

Conventional MRI usually employs spin-echo phenomena to produce T1- and T2-weighted pulse sequences, which are associated with high signal and good tissue contrast and resolution. However, fMRI requires a greater sensitization to the tiny differences in magnetic field caused by differing blood oxygenation. Therefore, fMRI pulse sequences are weighted toward the T2* effect, which reveals these differences, but is associated with lower signal and poorer tissue contrast (5,6,33,34). Originally, single slice gradient (field)-echo pulse sequences with echo times of approximately 60 milliseconds and repetition times of 90 milliseconds with 120 repetitions were used, but in recent years EPI has become the sequence of choice (4,11,12,41). While gradient-echo imaging typically took 14 seconds to acquire data from a single slice, EPI can produce images in a single repetition time of 100 milliseconds or less, although image resolution is poorer than with conventional MRI (usually 64 × 64 compared with 256 × 256). Faster acquisition times mean that a stack of two-dimensional slices can be acquired to cover the entire brain within seconds. Because fMRI signal changes are larger at higher field strengths, studies are usually performed at 1.5 Tesla or higher (10,11,42–44), although studies at 1.0 Tesla have been published (45,46). The percentage change in signal intensity with standard 1.5 Tesla hardware can be improved by optimizing section thickness, echo time, and field of view during visual activation (43). However, during neuronal activation the fMRI signal has been shown to increase linearly and quadratically with field strength (24), making the use of scanners up to 4.0 Tesla desirable (34,41). These scanners offer better spatial resolution but are technically more difficult to use. High field strength imaging at 4.0 Tesla provides an increased contribution from the venous and capillary bed and avoids contributions from large venous vessels or inflow effects from large arteries, which are undesirable because of their poor spatial correspondence with the actual site of neuronal activations (33,34). The increased importance of the susceptibility difference between deoxygenated and oxygenated blood at higher field strengths was illustrated with activated image intensity up to 28% at 4.0 Tesla but only up to 7% at 1.5 Tesla (41). Easily detectable signal increases of 5% to 20% were observed in area V1 at 4.0 Tesla, with signal increases that were predominantly restricted to areas containing grey matter (5,6). Nevertheless, some workers hesitate to use higher field strengths because of potential clinical adverse effects on volunteers and increased image artifacts caused by susceptibility effects.

Although EPI adds the further dimension of improved temporal resolution with images of brain function almost in real time, the spatial resolution is not as good as with gradient-echo fMRI (typically 64 × 64 cf. 128 × 128). A method of multislice interleaved excitation cycles (47) allows the acquisition of activation maps at multiple planes within total imaging times of a few seconds. By using a further specific method, it is possible to obtain a three-dimensional data set of the visual cortex in 20 seconds (48). EPI and signal targeting with an alternating radio (EPISTAR) frequency technique is a rapid, noninvasive means of creating qualitative maps of CBF with signal intensity changes that range from 13% to 193% (41). Using gradient-echo and spin-echo EPI at 3.0 Tesla, the greater microvascular selectivity of high-resolution spin-echo imaging enabled distinct activation patterns sensitive to stimulus motion to be detected in area V1/V2 that were not apparent with gradient-echo imaging (7).

Visual stimulation takes various forms, including flashing lights, red light emitting diodes (LED) mounted in goggles, conventional full field alternating black and white checkerboard patterns (sometimes modified into hemifields, wedges, or circles), and video and cine-film presentations. Modifications may be made to luminance, contrast, color, spatial, and temporal frequency, and so on, and the stimuli may be viewed under different conditions of attention, emotion, drug effects, and so on. Higher visual functions, such as appreciation of color, object and face recognition, movement and conscious perception, and others, may be assessed using appropriate experimental paradigms. A binocular fiberscope (49) can be used to relay high-resolution images of cathode ray tube displays from an adjacent room to an observer lying in a scanner, with a display of accurately controlled
To provide high-quality visual stimulation within the intense magnetic field of the MR scanner, a custom Maxwellian-view optic system (50) has been designed to project images directly onto the retina of subjects. This visual stimulator offers the particular advantages of a large field of view (60°) with a binocular stereoscopic display. The stimulation frequency dependence of fMRI visual activation was found to agree with previous PET studies, when the largest signal response occurred at 8 Hz (4). A simple visual experimental set-up used at the Institute of Neurological Sciences, Glasgow, is illustrated in Figure 2. The projection apparatus (a video projector or liquid crystal display projection panel on an overhead projector) projects the computer-generated stimuli through the observation window into the magnet room. The image falls onto a translucent screen, which the subjects view through a mirror inclined at 45° above their eyes. Because the distance between the subject’s head and the projection apparatus is approximately 7 m, an additional optical lens is required to reduce the size of the projected image. The available field of view is restricted by the MRI head coil and the bore of the magnet.

During a typical fMRI examination, images are collected at varying intervals over a period of several minutes during activated and resting conditions. In its simplest form, measurement of the activation signal involves subtraction of resting images (e.g., in total darkness) from activated images (e.g., on exposure to a flashing alternating black/white checkerboard). Because of the small size of the signal change, collection of many images improves the statistical reliability of the data. Simple subtraction of images acquired at baseline from activated images should theoretically define only areas of the brain in which the CBF has changed. Unfortunately, this process will yield artifactual areas of activation because of small involuntary movements of the subject’s head during image acquisition (24,25). In addition, the signal from blood in arterial vessels will vary depending on the part of the cardiac cycle during which the image is acquired. To reduce the contribution from these artifactual factors, it has been necessary to resort to advanced statistical approaches. Essentially, the application of the stimulus (on, off, on, off, etc.) has a time course, which may be represented as a simple “box-car” shaped function, and should be correlated in a time-series sense with the activated signal changes on a pixel-by-pixel basis (see Fig. 3). Image elements showing a signal increase every time the stimulus is applied will be highly correlated, whereas pixels overlying arterial vessels may coincidentally show signal increases on one or two occasions. By setting high statistical probability levels (typically \( p < 0.005 \)), it is possible to filter out these latter artifacts to a large degree. Various statistical packages have been developed to cope with these problems (51,52). After identification of an appropriate ROI (e.g., area V1), an idealized box-car function graph is compared to the signal changes, which should temporally correspond to the visual stimulus (Fig. 3). fMRI responses are slow when compared to changes in neural activity (e.g., the onset of a visual checkerboard pattern evoked a signal response that was delayed by 1 to 2 seconds and reached 90% of peak in 5 seconds with a slightly slower return to baseline) (50). The signal changes are delayed (rise-time) by the hemodynamic responses of the subject with blood flow taking up to 9 seconds to reach a plateau level after application of the visual stimulus or to fall to baseline values after its removal. This time-lag must be taken into account during the data analysis. Signal responses in the presence of noise may be detected using cross-correlation techniques and verified by statistical parametric mapping (51,52). Fuzzy cluster analysis has proved to be robust and efficient in the separation of functional brain activation from noise or other sources and when used in combination with an appropriate model calculation allows quantification of flow and BOLD contributions in areas with different vascularization (53).

It is possible to modify fMRI to produce recordings that are separately sensitized to cerebral blood oxygenation (CBO) and CBF (54). The duration of the visual stimulus used is important because CBF-sensitive recordings appear to remain elevated during the entire stimulation period, but in some CBO-sensitive recordings a signal decrease occurs after prolonged stimulation ranging from 1 to 6 minutes (13,54–59). However, others have not confirmed this signal decrease (60,61). As the

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**FIG. 2.** Experimental set-up in which the subject views through an inclined mirror above both eyes the stimulus projected from an outer room on to a translucent screen outside or inside the magnet bore.

**FIG. 3.** An idealized box-car function graph compared with the activated signal in the occipital cortex in response to an alternating black and white checkerboard at 8 Hz.
acquisition of more images improves the statistical reliability of the data, prolonged stimulation may be desirable, but only if there is no decrease in the relatively small activation signal. The discrepancy in these findings may represent different experimental paradigms and recording techniques, but the issue is unresolved.

Another major concern is the reproducibility of the activated signal. The application of adaptive correlation thresholds resulted in reasonable reproducibility in repeated single subject studies, but reproducibility across groups was poor (62). Test-retest analysis (63) of the activated area in the human visual cortex in 18 volunteers showed significant variability, both intersubject and intrasubject. However, using fuzzy cluster analysis intertrial reproducibility for repeated single subject studies was improved, but dependent on signal-to-noise ratio, motion artifact, and subject cooperation (64). A study of within-subject reproducibility of visual brain activation using EPI in 10 healthy subjects examined on three occasions concluded that measures of brain activity were reasonably reproducible on a routine clinical EPI system (65). Nevertheless, there were difficulties in separating the contributions of motion, repositioning errors, and true physiologic changes. High reproducibility of fMRI studies is important in the development of potential clinical applications. It is difficult to compare published data quantitatively owing to differences in sequence design and parameters, as well as statistical methods applied to enhance function-related image contrast. Technical, methodologic, and physiologic factors influence the variability of signal enhancement and the apparently activated area size. These should be taken into account in the interpretation of fMRI data quantitatively (62) and require further exploration.

Because of the irregularities of the surface of the human cerebral cortex and the variations from one individual to the next, it has been difficult to illustrate the activated images. An early spatial topographic technique in the visual cortex involved the application of a cortical ribbon along the 1.5- to 3-mm thick striate cortex to incorporate the subject-unique enfoldings (66). More recently, to compensate for the convolutions of the cortical gyri and sulci, reconstructions of the cortical surface have been developed using computational mapping (67). Surface base visualization involves reconstructing cortical surfaces and displaying them along with associated experimental data in various complementary formats, including three-dimensional native configurations, two-dimensional slices, extensively smooth surfaces, ellipsoidal representations, and cortical flat maps. In particular, this approach allows unfolding of the cortical sulci and representation of foci of cortical activity in a flattened two-dimensional mapping format. Because individual cortical areas vary in size by a factor of at least two and many areas are categorized by internal compartments or modules whose total number and dimensions vary across individuals, it would be unrealistic to expect functional correspondence to be identified more precisely than within a few millimeters for human cortex.

**MODIFICATION OF ACTIVATION SIGNAL.**

Because the amplitude of the activation signal is relatively small and difficult to detect against background noise, it is important to be aware of potential modifying factors. These include sex, attention, emotional state, ocular dominance, luminance contrast, and duration of stimulus.

Among 38 healthy subjects (20 males and 18 females), males were more likely than females to have an undetectable MR signal change after photic stimulation (68), but in a study of 16 healthy young subjects (8 male and 8 female), the signal response in area V1 to binocular photic stimulation was 38% lower in females than in males and much of the difference was lateralized to the right hemisphere (69). However, hemoglobin levels were not measured in these studies, which is regrettable because the BOLD fMRI response may be particularly sensitive to hemoglobin concentration (it is the iron within heme that provides the contrast in the MR signal intensity, and in general women have a lower hemoglobin level than young men).

During repeated presentations of identical visual motion stimuli (70), only the attentional component of the task was varied and attention-related enhancement of cortical responsiveness was evident in extrastriate and striate areas. Attention-related activity was demonstrated in area V1 when attention was selectively directed to one side of a moving wedge (the attention condition) compared with passive viewing of the wedge (the passive condition) (71). Activation of area V1 was found to be higher in the attention condition. In divided-attention and direction-attention tasks, early visual processing mechanisms in the prefrontal cortex were apparently influenced by an attentional system in the temporoparietal areas (72). Attention to visual motion (70) increased the responsiveness of the motion-selective extrastriate area V5 (73,74) and the posterior parietal cortex (75). Alternating attention between heard or seen numbers modulated corresponding activation signals in the auditory and visual cortices (76).

Emotional arousal, induced when subjects viewed a series of pleasant, neutral, or unpleasant pictures, produced significantly greater occipital activation (77). After determination of ocular dominance by the near-far alignment test, the dominant eye appeared to activate a larger area of area V1 than the nondominant eye (78). Increased activity in area V1 cells accompanied increased luminance contrast after stimulation with a single red LED covering 2° of the subject's visual field (79). Using a linear systems analysis of responses in area V1, the V1 signal increased monotonically with stimulus contrast (80). As mentioned previously, the duration of the stimulus may modify the size of the activation signal, but this finding is controversial because it has been identified by some authors (54-59) but not confirmed by others (60,61). The reason for this discrepancy has not been explained but may reflect contributions from factors other than the BOLD effect (e.g., the differential sensitivity of EPI and gradient-echo fMRI to flowing...
blood, rather than simply its oxygenation). Most studies have been carried out on young adults and, therefore, the literature does not contain information on the effect of age on the activation signal.

LOCALIZATION OF FUNCTIONS

Because of the robust and reproducible responses found in the occipital cortex during fMRI, considerable attention has been focused on the striate and the extra-striate cortex. Areal boundaries outlining V1, V2, V3, VP, V3a, V4, and V4v have been defined and higher visual functions such as recognition of objects, colors, faces, and so on have been localized. Because it is impossible to image the stria of Gennari, a varying contrast technique has been used to recognize activation confined to the striate cortex (81).

Retinotopic Representation

Data from human lesional studies show that neurones within area V1 are retinotopically organized after a roughly polar coordinate system (82,83). Movement from posterior to anterior in the striate cortex represents the center to the periphery of the visual field, a retinotopic dimension referred to as eccentricity. Movement from the inferior to the superior bank of the calcarine fissure represents shift from the superior vertical meridian through the horizontal meridian to the lower vertical meridian, a retinotopic dimension referred to as polar angle.

To map polar angle (i.e., angle from the center of gaze), subjects viewed a slowly rotating semicircular checkerboard stimulus, and to measure eccentricity (i.e., distance from the center of gaze), an expanding checker annulus (Fig. 4) (84). Neurones responding to stimulation at different locations in the visual field were activated at different times during the stimulus sequence, and corresponding differences in the temporal phase of the fMRI response identified the retinotopic location represented by each active site in the brain. Cortical locations of neurones responding to stimulation along the vertical or horizontal visual field meridians were charted on three-dimensional models of the occipital cortex and an unfolded map of the cortical surface produced in six subjects. The topography of visual areas V1, V2, V3, VP, and parts of V3a and V4 were consistent with the organization of these areas in macaque monkeys.

Using similar phase-encoded retinal stimulation, visual activation responses were recorded by EPI and analyzed with a Fourier-based method (85). The resulting volume data set was then sampled with a cortical surface reconstruction made from high-resolution structural MR images collected separately from each subject. The cortical surface containing the data was unfolded and analyzed with the visual field sign method, which automatically and objectively outlines areal boundaries, adjacent areas having the opposite field sign distinguished by mirror image and nonmirror image representations. Through a combination of multislice fMRI, stimulus phase-encoding and Fourier analysis, cortical surface reconstruction, and visual field sign, the retinotopic organization of visual areas V1, V2, VP, V3, and V4 was reconstructed in two dimensions with accurate delineation of their borders. Cortical magnification curves for striate and extra-striate areas were determined and humans appeared to have a greater emphasis on the center of gaze than their monkey counterparts.

After stimulation with spatially alternating flickering check stimuli in the form of iso-polar angle wedges, iso-eccentricity rings, and circles of equal polar-angle diameter (Fig. 4), the wedges produced parallel stripes of roughly equal width in V1, the rings of radically varying widths produced stripes of roughly equal width oriented approximately orthogonal to them, and the circles produced circular activity patches of roughly equal cortical width (81). The location of the blind spot was demonstrated by testing subjects binocularly and monocularly with a field of scaled, black and white flickering checks, when it was found that the blind spot lay just inferior to the cortical representation of the horizontal meridian at around 15° eccentricity. The size of the blind spot was generally consistent with the human cortical magnification factor in area V1 and with the width of the blind spot representation in human histologic material (86). This study demonstrated that area V1 could be activated preferentially to extrastriate areas by manipulation of luminance contrast and presentation of radial gratings alternating between 6% and 100% contrast. Evidence for orientation selectivity in V1 was provided by measuring transient fMRI increases produced at the change in response to gratings of different orientations. The band width of the orientation “transients” was approximately 45°.

Using an alternating black and white checkerboard to create simple visual stimuli that generated continuous traveling waves of neural activity in the visual cortex, activity could be localized to within 1.1 mm (87). From measurements of the motion of the traveling wave, the borders between retinotopically organized visual areas were identified and striate cortical positions related to visual field eccentricity. The foveal response was apparent in the posterior striate cortex and increasingly anterior locations responded to increasingly eccentric stimuli. Retinotopically organized responses extended along a 3- to 4-cm strip of striate cortex, although the stimulus only extended 12°. Retinotopic representation agreed with previous human lesion studies in the revised representation of the visual field hypothesis and electrophysiological data from nonhuman primates.

The representation of the (ipsilateral) visual field in 12

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FIG. 4. Checkered annulus, wedge, and rotating semicircle used to measure eccentricity and polar angle.
subjects appeared to reveal activity along the vertical meridian in retinotopic areas and in two large branches anterior to that, in presumptive higher-tier areas (88). Human area V3a was found to have a retinotopy similar to that found in macaque monkeys providing a continuous map of the contralateral hemifield immediately anterior to area V3, with a unique retinotopic representation of the upper visual field in the superior occipital cortex (89).

A view of the retinotopic representation in the occipital cortex is illustrated in Figure 5, constructed from activation changes in healthy volunteers (90), and contrasted with homologous areas in the macaque.

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![Image](image_url)

FIG. 5. Location and topography of presumptive visual areas in human and macaque cortex. (A & B) One representative cortical hemisphere of human brain in the normal (folded) state, based on high-resolution “anatomic” magnetic resonance images. Visual areas have been rendered in pseudocolor onto the surface, based on data from functional magnetic resonance imaging (fMRI) as described later. (C) The same anatomic and functional data depicted in “flattened” cortical format. Additional areas (bounded by red borders) are based on data from other subjects and were added for completion. Based on quantitative differences in cortical curvature, the locations of gyri and sulci in the folded brain depicted in A and B are represented in light and dark gray, respectively, in the flattened representation in C. For comparison, (D) shows the corresponding flat map from a macaque monkey, based on previously published data (136). Both flattened maps are taken from the right hemisphere, which was artificially split along the length of the calcarine fissure (approximately the horizontal meridian representation in V1). Borders of human visual areas are presumptive. However, each cortical visual area in A, B, and C has been reliably produced in approximately the same cortical location (with similar topographic relationships to surrounding areas, likewise defined) in several scan sessions in at least four subjects (usually many more), in response to the same visual stimulus or set of stimuli. Names for human visual areas have been adopted from apparently corresponding areas in macaque when there is topographic and functional evidence of homology (for example, V1, V2, V3, ventral posterior (VP), V3A, and middle temporal area (MT or V5)); this is qualified when evidence for homology is encouraging but undefined (for example, in the case of the posterior division of dorsal medial superior temporal area (pMSTd)). Otherwise, new names have been invented (i.e., lateral occipital [LO], SPO, and LSPO). Presumptive corresponding areas in the two primates are assigned the same color on the map. The foveal representation is a shared strip connecting most of the retinotopic areas and is centered roughly at the star.

Based on fMRI data and inferences from the connectional hierarchy in macaques (136), the human areas are grouped into three broad categories: retinotopic (blues and purples); parietal (greens); and temporal (yellow to red)—such categories are heuristic and tentative. Subjects were scanned in a 1.5-Tesla magnetic resonance imager, retrofitted with echo-planar imaging. In each 8-minute 32 second scan, 2,048 images were collected (repetition time (TR) = 4 seconds) in multislice mode (16 slices; 4-mm thick) at 3 x 3 mm resolution, using a bilateral surface coil (covering occipital and posterior temporal and parietal lobes) and an asymmetric spin-echo sequence (echo time (TE) = 70 milliseconds; offset = 25 milliseconds). Visual stimuli were presented to subjects within the magnet, with an extensive field of view. Phase-encoded, retinotopically varying stimuli (thinner rings. A set of black-and-white images of objects or faces, compared with scrambled versions of the same objects or faces, were used to activate area LO selectively, again in the same subject. Some variability was observed in the location of object-selective activity across individuals. Area LSPO responds selectively during saccade tracking, but not fixation, in near-total darkness. Area SPO is activated by the coherent motion of random, low-density dots, compared with random motion of the same set of dots, with otherwise identical motion parameters. In some subjects, area MT (V5) can be reliably and selectively activated by the motion coherence test and by tests for greater interhomotopic activation. The topography of human cortical areas is generally similar to that in macaques, except for an overall expansion; however, there are some noteworthy differences. 1) Human maps contain a posterior anterior retinotopic area (V4a) and a nonretinotopic, form-related area (LO) between MT (V5) and VP, but there is no clear area border corresponding to the border between V4a and LO in macaque maps. 2) There is proportionately more area between MT (V5) and foveal V3 and VP in human compared with macaque maps. 3) Human V3 and VP are proportionately several times wider than macaque V3 and VP. The assignment of separate names (V3a compared with VP) to mirror-symmetrical, quarter-field representations (otherwise known as superior and inferior arms of V3) is based entirely on macaque data; functional differences have not been reported between these two areas. In C, linear and angular distortion caused by flattening is minimized and averages approximately 15% overall (84); the corresponding distortion in D is presumably similar (138). Scale bars, 1 cm. Reprinted from Toddell RBH, Dale AM, Sereno MI, Malach R. New images from human visual cortex. In: Trends in Neurosciences, Vol. 19, 1996, 481–9. With permission from Elsevier Science.
visual field in the striate cortex has not been clarified, but study of the central 11°, 19°, and 56° confirms the increased emphasis placed on the representation of the central 10° in at least 50% of the striate cortex posteriorly according to the revised representation hypothesis (91). However, in the 11° and 19° conditions, some activation spread anteriorly to the parieto-occipital/calcineurine fissure junction, indicative of unknown behavioral patterns in the striate cortex. Clinically, further knowledge of the precise retinotopic organization of area VI could eventually lead to objective perimetry using fMRI.

Color Recognition

Activation by an array of six colored circles and their after-images suggested that the fusiform gyri play a critical role in human color perception (92). In a repetitive stimulation protocol, isoluminant chromatic or isochromatic luminance modulation was alternated with steady light of the same mean chromaticity and luminance as a reference condition. Color-sensitive activation was observed in collateral sulci and area V1 (93). Color tuning in response to a large number of colors suggests that color signals relevant for perception are included in a large population of areas V1 and V2 neurons. The strongest response is to red-green stimuli receiving opposing inputs from L and M retinal cones (94). Color vision may be considered in terms of perception and imagining of color. Using a colored and grey scale Mondrian display and contrasting a relative color judgement with a spatial task requiring the generation of mental images, it was shown that color perception activates the posterior fusiform gyrus bilaterally (V4), plus the right anterior fusiform and lingual gyr, striate cortex (VI), and left and right insula. Color imagery activated the right anterior fusiform gyrus, left insula, right hippocampus, and parahippocampal gyr, but not areas V4 nor V1. The findings suggest that the anterior fusiform and parahippocampal gyri and the hippocampus are the location for stored representation of colored objects (95).

Object Recognition

Convergence of visual cues in the form of motion, texture, and luminance contrast were demonstrated on the lateral aspect of the occipital lobe (LO complex) providing strong evidence for its role in object processing (96). There was preferential activation of LO by images of objects, when compared to a wide range of texture patterns. The "Lincoln" illusion, in which blurring of objects digitized into large blocks paradoxically increases their recognizability, significantly enhanced LO activation. However, LO did not seem to be involved in the final stages of the recognition process (97).

Face Recognition

During a face-matching task, there was a significantly increased MR signal in the ventral occipito-temporal cortex, extending from the inferior occipital sulcus to the lateral occipito-temporal sulcus and fusiform gyrus (98). Selective involvement of the fusiform face area in face perception has also been demonstrated (99). Comparing cerebral hemispheres, faces primarily activated the fusiform gyrus bilaterally, but there was greater activation in the right than in the left hemisphere (100).

Ocular Dominance

Ocular dominance was determined by means of the near-far alignment test, when stimulation of the dominant eye activated a larger area of V1 than the non-dominant eye (78). Ocular dominance in V1 resemble those of the single cell recordings of Hubel and Wiesel demonstrated when seven categories of response were identified, varying from left only to binocular only to right only responses. Using differential techniques neuronal activity in cortical columns raised the possibility of further mapping of specialized neurons in human visual cortex (101).

Motion Perception

Area MT cortex (the human homologue of the motion sensitive middle temporal area, MT or V5 of monkeys) responded selectively to moving compared to stationary stimuli, consistent with previous PET and anatomic studies. In addition, area MT has a much higher contrast sensitivity, particularly when compared with area V1. Using color varying stimuli and changes in luminance, activity in MT decreased at and near individually measured equiluminance, compatible with the psychophysical phenomenon that visual motion appears to diminish when moving color varying stimuli are equated in luminance. Activity in area MT appeared much less retinotopic than in areas V1, V2, V3, and VP (102). Viewing a stationary stimulus after adaptation to stimuli moving in a single local direction creates a visual motion after-effect of illusory motion, also known as the waterfall illusion, to which human cortical area MT (V5) is responsive in a direction-specific manner. The time course of the motion after-effect measured psychophysically was essentially identical to the time course of the fMRI motion after-effect (100). Motion perception studied when subjects viewed a stationary black and white grating, a moving grating, and a moving spot generated activation in the lateral occipitotemporal cortex (area MT). During pursuit, extraretinal signals may be received because the signal intensity during pursuit of the moving dot was greater than during viewing of the moving grating. This occurred despite the fact that the moving grating generated more retinal image motion, while signal intensity in the striate cortex was least during pursuit of the moving dot (104). Each of three different motion displays activated specific parts of the V5 complex, but also activated neighboring, although nonoverlapping, regions of the auditory cortex that are normally activated by the perception of speech (105). Motion boundaries produce a boundary specific signal that is retinotopically organized within area V1, but appears to be largely absent from the motion selective area MT-V5 (106). A region more activated by kinetic gratings than by luminance-defined gratings, uniform motion, or transparent motion, anatomically and functionally distinct from areas MT-V5, V3, and V3a but minimally overlapping the LO region, has been identified and appears to be genuinely
specialized for processing kinetic boundaries, created by discontinuities in motion direction (107). Various motion stimuli have been used to study the effects of first and second order motion. It appears that first order motion sensitivity is localized to area V1, whereas second order motion is represented in areas V3 and VP, and area V5 and possibly areas V3a and V3b are involved in further processing of motion information, including the integration of motion signals of both types (108). Human area V3a appears to be different from its macaque counterparts in being relatively motion-selective when compared with area V3 (89).

Eye Movements

Pursuit eye movements during visual motion perception, while viewing sequences of random dot motion and moving dots under conditions of fixation or pursuit, highlighted a motion-specific area in the lateral occipito-temporal cortex (V5). There was also activation in a region approximately 12 mm dorsal to area V5 (74).

Voluntary saccades in light or dark and imagined saccades with electro-oculogram monitoring produced significant activation of the frontal eye field (precentral and posterior medial frontal gyrus) in all conditions and the supplementary eye field (superior frontal gyrus) during the voluntary condition. In addition, voluntary saccades activated the primary visual cortex, but imagined saccades did not (109). During visually guided saccades, bilateral activity was detected in the occipital cortex, the precentral sulcus, and the deep region of the intraparietal sulcus. This intraparietal area borders areas 39 and 40 of Brodmann and apparently corresponds to the human parietal eye field (110).

Other Functions

Visual perception and visual imagery may share a common neural anatomic substrate. During recall of a visual stimulus, focal signal changes were detected in areas V1 and V2. It appears that processes involved in visual perception may also be applicable to visual imagery (111). When viewing the corners of a Kanizsa square, specific extrastriate regions primarily in the right hemisphere responded to illusory contour perception, an important aspect of perceptual grouping (112). On presentation of dissimilar images to the two eyes, perception alternates spontaneously between each monocular view (i.e., binocular rivalry occurs). Fronto-parietal areas appear to play a central role in conscious perception biasing the content of visual awareness toward abstract internal representations of visual scenes, rather than simply toward space (113). Mental image generation asymmetrically activated the visual association cortex on the left side (114). During a test of differential sensitivity to faces, letter strings, and textures, faces primarily activated the fusiform gyrus bilaterally, letter strings the left occipito-temporal and inferior occipital sulci, and texture portions of the collateral sulcus. Thus, different regions of ventral extrastriate cortex are specialized for processing facial features and letter strings and are intermediate between earlier processing in striate and peristriate cortex and later lexical, semantic, and associative processing in downstream cortical regions (100). String length contrast alone was sufficient to account for the activation pattern in the medial visual cortex by word-like stimuli, when contrasted with single characters (115).

METABOLIC EFFECTS

The behavior of the fMRI signal in the visual cortex has significant implications for our understanding of brain metabolism. PET studies have demonstrated that visual activation results in an increased CBF and hyperoxygenation, without a corresponding increase in the oxygen extraction fraction, but accompanied by an increased cerebral glucose metabolic rate (31). These features are compatible with anaerobic glycolysis. Furthermore, MRS studies on visual stimulation demonstrate increased glucose utilization with the accumulation of lactate in the visual cortex, which on continued stimulation subsequently declines, again indicative of anaerobic glycolysis initially (116,117). Therefore, it has been proposed that the initial MR activation signal represents an uncoupling between regional CBF and oxygenation and oxidative metabolism (i.e., anaerobic glycolysis), but the subsequent return of the activation signal toward baseline at an interval that varies from 1 to 5 minutes is indicative of a return to oxidative metabolism through cerebral autoregulation (54-59).

During prolonged activation of the visual cortex by a video presentation, CBO- and CBF-sensitive fMRI recordings were monitored separately (54). Oxygen-sensitive recordings displayed an initial signal increase, followed by a subsequent signal decrease extending over 4 to 5 minutes, and a signal drop at the end of stimulation. However, flow sensitive recordings demonstrated that the in-flow effect remained elevated during the entire stimulation period. Thus, gradually decreasing CBO despite persisting elevation of CBF reflected an accumulation of deoxyhemoglobin caused by progressive up-regulation of oxidative metabolism after prolonged stimulation. Dynamic uncoupling and recoupling of perfusion and oxidative metabolism were observed by measuring changes in glucose consumption, lactate production, and CBO during prolonged neuronal activation using dynamic MRS and fMRI (57). After visual stimulation, a decrease of steady-state glucose by 40% because of enhanced use by 21% was accompanied by a transient accumulation of lactate 2.5 minutes after stimulation onset. Again, nonoxidative glucose metabolism during functional activation was gradually complemented by a slow return to oxidative metabolism, with recoupling of perfusion and oxygen consumption at a new equilibrium. After stimulation of the visual cortex with photic stimuli of varying duration, a postactivation undershoot may occur during fMRI (54). However, the absence of an undershoot after longer stimulation periods provides further evidence of a gradual shift from an uncoupling between regional CBF and oxygen consumption toward a steady-state (118).
By contrast, other studies have suggested that the CBF and oxygen consumption remain constant during the entire time that primary visual cortical neurones are activated (60,61). In an fMRI study sensitized to flow and oxygenation changes as well as PET-sensitized to flow (60), several types of visual stimulation were used and flow and oxygenation were evaluated in separate time-course series as well as simultaneously using two different MRI methods. In most cases, the activation-induced increase in flow and oxygenation remained elevated for the entire stimulus duration, suggesting that flow rate and oxygen consumption remained constant during the activation period. In addition, a prolonged visual stimulation study using different MRI techniques and two different visual stimuli showed that the signal-time course from areas of significant activation remained largely elevated throughout the duration of stimulation, unaffected by the imaging method used (61). These data suggested that recoupling between blood flow and oxygen extraction was not a general phenomenon during extended visual stimulation.

The interpretation of the discrepancy in these findings is difficult, especially because different studies use different experimental paradigms and imaging sequences. However, this is an important issue that may, in particular, offer an explanation for the nature of the fMRI signal. Hopefully, further metabolic studies will provide a solution.

**CLINICAL USAGE**

fMRI may be used in preoperative neurosurgical planning. Two patients with complex partial seizures referable to the temporal and occipital regions showed significant signal intensity changes up to 15% between the activated and resting conditions during repetitive photic stimulation near the surgical targets (21). Systematic fMRI studies in patients with vascular malformations adjacent to the primary visual cortex demonstrated displacement of the activated region and hemispheric asymmetry in the number of activated voxels in the functional region, which appeared to reflect the anatomic and physiologic impact of the vascular malformation. Changes in fMRI findings after intervention monitored the consequences of therapy and paralleled clinical recovery (23).

After fMRI in two patients with a homonymous hemianopia, one after an established cerebral infarction and the other during the recovery phase from an episode of multiple sclerosis to a normal visual field, it was concluded that fMRI activation may prove to be a useful way of objectively measuring visual function. In the patient with infarction, the signal change was decreased on the affected side, whereas in the patient with multiple sclerosis the activations were within normal limits (119). In five patients with homonymous hemianopic visual field loss caused by retrochiasmal lesions, activation abnormalities were compatible with the visual field defect in three patients, but two patients with macular sparing showed symmetric responses (120). Dynamic susceptibility contrast imaging, also known as relative cerebral blood volume mapping, may provide further information about the hemodynamics after strokes. In a study of five patients with occipital infarction with visual field analysis, cortical activation mapping and dynamic susceptibility contrast imaging during full field visual stimulation demonstrated that fMRI techniques can accurately map functional and perfusion deficits and provide useful clinical information (14). Abnormal brain tissue function may extend beyond the limit of an infarct seen on conventional imaging, but by determining areas of spared cortex fMRI techniques may help to assess the efficacy of therapeutic interventions and improve rehabilitation strategies. After severe craniocerebral trauma affecting the optic radiations, a patient developed an incomplete macular splitting homonymous hemianopia with blind sight. The visual responsiveness of deafferented VI was examined, when ipsilesional VI displayed no stimulus-related signal change, but activation was observed in ipsilesional extrastriate cortex (121). Thus, blind sight does not appear to depend on deafferented striate cortex.

In seven patients with visual field loss caused by lesions of the optic nerve and the optic chiasm, there appeared to be a correlation with failure of activation in that part of the striate cortex corresponding to the central visual field defect (122). In a patient with optic atrophy but central visual field sparing, it was claimed that the cortical activation pattern corresponded to the visual field loss (123), but this finding has been disputed largely on the grounds of anatomic localization (124).

To determine the pathophysiology of dyslexia, fMRI was used to study visual motion processing in normal and dyslexic men (19). In all of the dyslexic patients, presentation of moving stimuli did not produce the same task-related functional activation in area V5-MT observed in controls. Stationary patterns produced equivalent activation nboth groups. The relationship between brain activity and reading performance was explored in dyslexic patients, who showed reduced activity compared with controls in the primary visual cortex and in a secondary cortical visual area (MT+) believed to receive a strong magnocellular (M)-pathway input (125). Significant correlations were found between individual differences in reading rate and brain activations; the results support the hypothesis for an M-pathway abnormality in dyslexia and imply a strong relationship between the integrity of the M-pathway and reading ability.

Consistent with a chiasmal crossing anomaly in albinism is the finding in albino patients that monocular stimulation caused predominantly contralateral activation, whereas control subjects had symmetrical patterns of activation (20).

In patients with schizophrenia, the mean signal intensity change in the primary visual cortex was significantly greater on photic stimulation than in normal controls, possibly reflecting structural brain changes or impairment of mitochondrial function or energy metabolism (16). In one patient with cortical Lewy body dementia who experienced persistent and vivid complex visual hallucinations, photic stimulation produced a normal bi-
lateral activation response in area V1 when he was not hallucinating, but limited activation during hallucinations (17). Depressed subjects were studied while using positively and negatively balanced visual stimuli before and after venlafaxine (18). Preliminary results suggested that fMRI would be useful to study emotional processes in normal and depressed subjects and to examine the mechanisms of action of antidepressant drugs. These studies are indicative of fMRI's potential for assessing brain abnormalities in psychiatric disorders and monitoring treatment.

Pharmacologic induction of vasodilatation by acetazolamide attenuated signal changes under photic stimulation, but there appeared to be a persisting autoregulatory responsiveness to functional challenge (126). After cocaine infusion, it was possible to map dynamic patterns of brain activation and provide evidence of dynamically changing brain networks associated with cocaine-induced euphoria and craving, which affected a number of brain regions including the occipital cortex (127). Although cocaine infusion produced a small but definite decrease in global cortical CBF, visual stimulation resulted in comparable signal increases in visual cortex before and after cocaine and saline infusion (128). The elucidation of the effects of drugs on the central nervous system could be an important future use of fMRI.

OTHER FUNCTIONAL IMAGING TECHNIQUES

While detailed comparison with other functional imaging techniques in the visual cortex is beyond the scope of this review, it is possible to profitably allude to a few studies.

Comparison with PET studies are interesting because it is known that the PET signal measures intraparenchymal changes in CBF. Primary visual cortical activation was evaluated using fMRI and H2-15O PET in six male subjects visually stimulated by means of red LED flash goggles. The PET technique demonstrated substantially greater relative signal change on visual stimulation than the fMRI technique. The fMRI signal changes were concentrated in loci around the periphery of brain parenchyma exhibiting increased radiotracer activity. It was concluded that signal changes using fMRI based on gradient-echo techniques reflected primarily phenomena occurring within small veins and under-represented activity intrinsic to brain parenchyma, while PET directly measured changes in metabolically related activity within the parenchyma. This finding suggested potential inaccuracies in localization of activated brain tissue using fMRI (129). However, functional activation maps for the visual cortex have been obtained at a spatial resolution almost two orders of magnitude greater than achievable by PET and within measuring times of a few seconds using gradient-echo imaging at 2.0 Tesla (130). Cortical areas associated with face perception identified by PET and fMRI were in similar anatomic locations, but in addition fMRI revealed interindividual variation with greater anatomic precision (98).

Comparison of activation findings with MEG and fMRI indicates that these techniques offer different, largely complementary capabilities. While fMRI offers excellent spatial resolution of <1 mm, MEG has a temporal resolution measured in milliseconds. It is possible to treat MEG and fMRI data within a unified computational framework. fMRI precisely defining the locations of activation to regions and MEG the temporal dynamic (131). MEG studies of retinotopic representation in conjunction with anatomic MRI correlation have been carried out by presenting small pattern stimuli near the vertical and horizontal meridians. The results suggested that the representation of the horizontal meridian did not necessarily correspond in a one-to-one manner with the base of the calcarine fissure. Significant individual variability in the details of how area V1 maps around the calcarine fissure was identified (132).

FURTHER DEVELOPMENTS

Using flow-sensitive fMRI with steady-state arterial water labeling, it is possible to measure the relative CBF increase during brain activation. On visual stimulation, CBF in the visual cortex increased by 17% to 35%. Such quantification facilitates comparative fMRI studies under different conditions (133). The use of magnetically variable tissue water proton spins as a freely diffusible tracer provides maps of absolute CBF changes (delta CBF). The individual mean values of delta CBF measured in five healthy volunteers ranged from 69 ± 18 to 99 ± 26 ml/minute per 100 g on visual stimulation with an alternating black and white checkerboard at 8 Hz (134).

Since the advent of fMRI, there has been a continual improvement in spatial and temporal resolution. Using the latest scanners, it is possible to record activated signals with a spatial resolution of <1 mm and a temporal resolution of <1 second. Continued technologic development may enhance this performance. However, further investigations are required to localize in terms of microvessels or macrovessels the magnetic effect responsible for the fMRI image and to develop understanding of the coupling between neuronal activity and CBF and oxygenation. Comparison with PET, MRS, and NIRS may elucidate some of the cerebral metabolic changes in response to activation experiments and in disease states. While functional imaging studies can localize cortical activations in response to different experimental paradigms, it is impossible to image the white matter interconnecting pathways (e.g., the fronto-parieto-occipital connections during viewing of a moving scene). Nevertheless, with improved temporal resolution, it may be possible to infer the nature of higher cortical connections during activation processes. In general, fMRI is constrained to investigation of sustainable and reproducible activation, but attempts are being made to examine single events rather than repeated stimuli by more resolvable temporal analysis. The technique of magnetic source imaging combines the high spatial resolution of fMRI and MRI with the high temporal resolution of MEG in this respect (135).
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Tuberculous Neuroretinitis

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Objectives: To describe a patient with tuberculous neuroretinitis.

Materials and Methods: Retrospective case report.

Results: We describe a 43-year-old otherwise asymptomatic woman with a known exposure to tuberculosis who had unilateral optic disc edema and a partial macular star (neuroretinitis). This was followed approximately 1 year later by the development of an exudative retinal detachment in the setting of bilateral multifocal choroiditis. Laboratory testing revealed a marked positive cutaneous reaction to purified protein derivative (PPD). Treatment with antituberculosis medicine alone resulted in prompt resolution of the choroidal infiltrates and complete flattening of the exudative detachment.

Conclusions: Tuberculosis should be considered in the differential diagnosis for patients with neuroretinitis.

Key Words: Choroiditis—Exudative retinal detachment—Optic disc edema—Macular star—Serous retinal detachment—Tuberculosis.

Neuroretinitis is a clinically unique form of optic neuropathy characterized by optic disc edema in the presence of peripapillary and macular subretinal and intraretinal exudates, often forming a complete or partial macular star (1–3). Vitreous inflammation is typically mild. Most cases are unilateral, and an afferent pupillary defect is frequently present. Recurrences, although uncommon, can occur (4).

Organisms reported to cause neuroretinitis include Bartonella henselae (5–10), Treponema pallidum (11–14), Toxoplasma gondii (15–17), Trachoma curis (18,19), Borrelia burgdorferi (20), Leptospira (1), and paramyxovirus (21). Rarely, patients with Mycobacterium tuberculosis-associated optic disc edema and retinal exudates have been described (22), but only in the setting of large peripapillary choroidal lesions (23,24). We describe a patient with evidence of systemic M. tuberculosis infection who initially had isolated neuroretinitis.

CASE REPORT

A 43-year-old woman, a Mexican immigrant, complained of shadows in her right eye for 2 months. The ocular history was unremarkable. Medical history was significant for exposure to a child at home who had been treated for pulmonary tuberculosis. Review of systems was otherwise noncontributory. Best-corrected visual acuity was 20/20 on the right and 20/20 on the left. No afferent pupillary defect was present. Intraocular pressure was normal. Examination of the left eye was unremarkable. Examination of the right eye revealed moderate optic disc edema and subretinal exudates forming a partial macular star (Fig. 1). Syphilis serologies, angiotensin-converting enzyme level, and a chest radiograph were negative. The patient was lost to follow-up, but returned 13 months later complaining of decreased vision in the left eye. Best-corrected visual acuity was 20/25 on the right and 20/200 on the left. No afferent pupillary defect was present. Fundus examination revealed mild vitreous inflammation, moderate optic disc edema, and multifocal choroiditis in each eye (Figs. 2A & B). A localized exudative retinal detachment involving the fovea was present on the left (Fig. 2B-D). Purified protein derivative (PPD) skin testing produced 15 mm of induration with overlying dermatoysis (Fig. 3). A repeat chest radiograph was negative. Examination of the cerebrospinal fluid was normal. Treatment with systemic isoniazide and rifampin resulted in prompt resolution of the choroidal infiltrates and complete flattening of the exudative retinal detachment within 3 months. No corticosteroids were given. Visual acuity at last follow-up was 20/25 in each eye.

DISCUSSION

M. tuberculosis is an infrequent but well-recognized ocular pathogen (22). Tuberculous optic neuropathy is one of the best described complication of systemic infection and is almost always retrobulbar and usually observed as a complication of tuberculous meningitis (25,26). In contrast, anterior optic neuropathy caused by tuberculosis is rare and usually appears as a
FIG. 1. A photograph of the right fundus at initial presentation reveals neuroretinitis, characterized by moderate optic disc edema with subretinal exudates in a partial macular star pattern.

consequence of adjacent or nearby choroiditis (23, 24). Our patient was unique in that her neuroretinitis initially occurred in isolation. Our patient was also noteworthy in that she developed a localized exudative retinal detachment over an area of tuberculous choroiditis, an uncommon but reported cause of serous elevation of the retina in patients with uveitis (24, 27, 28).

The diagnosis of ocular tuberculosis is often difficult (22). Histopathologic or culture identification of acid-fast bacilli from ocular biopsy specimens offers the strongest evidence for infection (28, 29–32), but is usually reserved for severely damaged or end-stage eyes. Polymerase chain reaction-based amplification of M. tuberculosis-specific DNA sequences from ocular fluid specimens provides an alternative (32–35) and, perhaps less risky, technique for identifying infection, but is not widely available and has yet to be standardized with regard to sensitivity or specificity. In the absence of such direct identification of M. tuberculosis or its DNA from ocular tissues, the diagnosis of ocular tuberculosis remains presumptive and is based on clinical evidence of concurrent or past pulmonary or extrapulmonary infection. Findings in support of the diagnosis of ocular tuberculosis can include a positive chest radiograph or sputum sample, a positive PPD (particularly when >15 mm), a positive urine, blood, synovial or cerebrospinal fluid culture, a positive biopsy of a suspicious extracocular tissue site, or clinical improvement in response to antituberculous therapy. We chose not to perform an ocular biopsy or fluid aspirate in our patient given our strong suspicion of tuberculosis based on her known history of exposure to tuberculosis, on her markedly positive PPD, and on her prompt and complete response to antituberculous medications without the use of local or systemic corticosteroid therapy. Although the chest radiograph was negative in our case, similar patients with ocular tuberculosis and a positive PPD but negative chest radiograph have been described (23, 28, 36). Ocular tuberculosis can even occur in the complete absence of detectable systemic infection (29, 30, 34).

In summary, M. tuberculosis infection can cause neuroretinitis and should be considered in any patients with systemic signs or symptoms suggesting tuberculosis, with a known exposure to other tuberculosis, or who come from or have traveled to areas where tuberculosis is endemic.
FIG. 2. Right (A) and left (B) fundus photographs taken 13 months after initial presentation show mild vitreous inflammation, moderate optic disc edema, and multifocal choroiditis in each eye. An exudative retinal detachment overlying a particularly large area of choroiditis and involving the fovea is present on the left (arrowheads). Early (C) and late (D) fluorescein angiograms taken on the left eye show progressive staining of the area of subfoveal choroiditis.

FIG. 3. A delayed-type hypersensitivity reaction to purified protein derivative measured at 15 mm (arrowhead). Overlying dermatolysis is evident.
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High Altitude Retinopathy

Andrew G. Lee, MD, Alfonso E. Aldama, MD, and Richard L. Harper, MD

Two previously healthy white male neurosurgeons (AEA, RLH) ages 40 and 43 years old returned to Houston after mountain climbing January 30, 1989, on Mount Aconcagua in the Andes mountain range of Argentina (the highest point in the Western hemisphere). Ophthalmologic examinations before the trip were entirely normal. Retinal photographs taken 8 days after exposure at the altitude of 6,986 meters (Figs. 1 and 2) revealed asymptomatic retinal hemorrhages consistent with high-altitude retinopathy. The remainder of the ophthalmologic examination was normal in both individuals. Serial ophthalmoscopic examinations revealed gradual resolution of the intraretinal hemorrhages without ocular sequelae. Magnetic resonance imaging of the head was normal in both patients. Butler et al. prospectively performed comprehensive eye examinations and fundus photography at sea level before and after 6 weeks of

FIG. 1. Fundus photograph of the left eye in climber one with peripapillary flame hemorrhages.
exposure to altitudes from 5,300 to 8,200 meters. Asymptomatic intraretinal hemorrhages were found in five eyes of four climbers. An additional eye in one climber had a central retinal vein occlusion with a vitreous hemorrhage and count fingers visual acuity. Higher baseline intraocular pressure and the use of nonsteroidal antiinflammatory medications were found to be significant risk factors for altitude retinopathy (1).

REFERENCES

The pregeniculate afferent visual system was the focus of many interesting reviews, reports, and investigations during the second half of the year 1998. This semiannual review includes the months of June through December 1998. The following table of contents has been provided for ease of reference to the topics presented:

1) EVALUATION OF THE AFFERENT VISUAL SYSTEM
   a) MR Imaging
   b) Visual Field Testing
   c) The Puffrich Phenomenon

2) NEURO-OPHTHALMOLOGY AND THE RETINA
   a) Cancer-Associated Retinopathy (CAR)
   b) Tamoxifen Retinopathy
   c) Creutzfeldt-Jacob Disease
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3) THE OPTIC NERVE
   a) Anterior Ischemic Optic Neuropathy
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   d) Infectious, Inflammatory, and Post-Surgical Optic Neuropathies
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4) THE OPTIC CHIASM AND BEYOND
   a) Pituitary Adenomas
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   c) Band Optic Atrophy
   d) Sellar Arachnoid Cysts
   e) Traumatic Lateral Geniculate Hemorrhage

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hemianopia was the predominant defect. Both patients had normal MR and CT imaging of the brain and orbits; electoretinograms and visual evoked responses were also normal. Binocular Goldmann perimetry was useful in both cases, demonstrating constriction ipsilateral to the monocular defect despite the patient having both eyes open for testing. However, both authors emphasized the importance of considering organic disease since true field abnormalities may be masked by nonphysiologic perimetric findings.

Patterns of "hysterical hemianopia" were also the topic of an extensive review by Keane of 454 patients with "pseudoneurologic" signs (3). In these patients, whose evaluations spanned a 25-year period, most functional visual field defects were readily documented using confrontation techniques. Monocular temporal defects, which persisted on binocular testing, were the most common pattern of functional hemianopia (58%), followed by monocular blindness (20%). Keane (3) stressed that despite advances in the use of computerized perimetry, confrontation techniques, particularly using double simultaneous finger counting, continue to be helpful for documenting functional visual field defects.

The Pulfrich Phenomenon

The Pulfrich phenomenon, a sensitive sign of unilateral optic neuropathy, may correlate with difficulties in performing certain visual tasks, such as judging distances while driving. The development of a simple yet highly predictive bedside test for the Pulfrich phenomenon was recently undertaken by Mojon et al. (4). They examined 18 patients with unilateral optic neuritis, 2 normal volunteers with optic neuropathy simulated by neutral density filters, and 90 normal control subjects using the "swinging pen test." As the name suggests, this new test involves the manual oscillation of a black pen in front of a white background (a lab coat) by the examiner at a fixed distance from the patient (Fig. 1). The mechanical pendulum test, a standardized method of detecting the Pulfrich phenomenon, was also performed for all participants in the study. Results of the swinging pen test were compared to those of the mechanical pendulum test with respect to the magnitude of perceived oscillation (the degree of perceived elliptical rotation of the pen or pendulum). For the two normal volunteers with simulated optic nerve disease (neutral density filters), high correlations (r = 0.92–0.96) were found between the magnitudes of simulated oscillation using the swinging pen versus mechanical pendulum test. These magnitudes also correlated well among 18 patients with optic neuritis (r = 0.90), demonstrating that the swinging pen test can be useful in detecting degrees of disease severity. Since none of the 90 normal control subjects perceived a Pulfrich phenomenon using the swinging pen test or the mechanical pendulum test, the positive predictive value of the new swinging pen test was 100% among the patients with optic neuritis. This new test, which also demonstrates excellent interobserver reliability, provides a simple, familiar, and potentially useful adjunctive method for detecting optic neuropathies.

FIG. 1. The swinging pen test. The examiner holds the thumb of one hand in the region of the epigastrium pointing toward the head. A black pen is held with the other hand directly above the thumb and oscillated in a plane perpendicular to the viewer. The observer looks at the thumb and describes how the pen oscillates. Normal subjects report the oscillation to be in one plane. If an elliptical movement is perceived, the thumb can be moved toward the patient to determine the size of the illusion. Reprinted with permission from: Mojon DS, Rosier KM, Oetliker H. A bedside test to determine motion stereopsis using the Pulfrich phenomenon. Ophthalmology 1998;105:1337–44.

NEURO-OPHTHALMOLOGY AND THE RETINA

Cancer-Associated Retinopathies

Whitecup and colleagues (5) presented the first known case of a patient with retinopathy and serum antibodies to a 23-kd antigen (recoverin) in whom an associated malignancy has not been found. As emphasized in an accompanying editorial by Keltner and Thirkill (6), the case description by Whitecup et al. (5) adds to our knowledge of immune-mediated retinopathies. In addition to comments regarding the mechanisms of cancer-associated retinopathies (CAR), Keltner and Thirkill (6) also provided a useful summary of recommendations for evaluation, serologic diagnosis, and treatment of CAR, stressing that our understanding of this condition is continuously evolving.

Tamoxifen Retinopathy

Treatments for systemic malignancies may also be associated with retinal dysfunction, as indicated in a recent report by Lee (7) of a patient with tamoxifen retinopathy. This 64-year-old woman developed painless visual loss in both eyes 5 years after surgical resection, local radiotherapy, and initiation of daily tamoxifen therapy for breast cancer. Visual acuities at presentation were 20/15 in the right eye and 20/60 in the left. Funduscopic ex-
dysfunction in patients with suspected CJD. The predictions in addition to crystalline retinopathy, including corneal opacity and decreased visual acuity.

Creutzfeldt-Jakob Disease

Visual signs and symptoms occur frequently in the setting of Creutzfeldt-Jakob disease (CJD), and may often be presenting features of this disorder. Because Creutzfeldt-Jakob (CJD) disease is a disorder characterized by pathologic changes within gray matter, DeSeze and colleagues (8) investigated the possibility of retinal dysfunction in patients with suspected CJD. The predictive value of noninvasive visual electrophysiologic testing, including electrotinography (ERG) and visual-evoked potentials (VEP), was examined in 41 consecutive patients. Twenty-four patients had definite (pathologically proven) or probable (meet published laboratory/clinical criteria) CJD, while 17 were diagnosed with other neurologic disorders (control patients). Fundus examinations were normal in all patients. ERG, performed in 19 of the 24 patients with CJD, demonstrated significant reduction in the amplitude of the B1 wave in patients with CJD compared with controls (p < 0.0005). Impairment of the B1 wave, with relative sparing of the A wave, correlated closely with pathologic findings demonstrated in the retinas of these patients, which included spongiiform changes in the outer plexiform and ganglion cell layers. The amplitude of the flash VEP was significantly increased in the CJD group (p < 0.0005), although there were no differences in VEP latencies. These findings are consistent with early dysfunction of inner retinal layers in patients with CJD; however, caution in the interpretation of a reduced B1 wave on ERG is also warranted since this finding may occur in the setting of other neurodegenerative diseases.

HIV-Associated Visual Loss

HIV optic neuropathy has been implicated as a cause of visual loss in some patients with human immunodeficiency virus (HIV). However, a recent report of a patient by Donahue (9) emphasizes that this diagnosis must be made with caution if an ERG has not been performed. A 35-year-old man had progressive visual loss in both eyes 12 years after diagnosis with HIV. Examination revealed reduced visual acuities (20/50–20/60), abnormal color vision, constriction of visual fields, attenuated retinal vessels, and bilateral optic disc pallor. Despite the absence of detectable virems in the patient's serum, his visual loss progressed during the next 6 months. An ERG demonstrated severe attenuation of rod and cone function, with reduction of the 30-Hz flicker and B-wave responses. The authors (9) appropriately indicate that CAR may be included in the differential diagnosis for this patient, and that the markedly abnormal ERG in this case was the key factor in excluding HIV optic neuropathy as the sole cause of visual loss.

Vascular Disease and the Retina

Episodic monocular visual loss may result from emboli, vasospasm, vasculitis, and, more rarely, arteriovenous malformations (AVMs) of the retina. Hardy and O'Day (10) presented a patient who developed a central retinal vein occlusion and visual loss in association with a retinal AVM. At the age of 20 years, she had first noted intermittent blurred vision in the right eye. A retinal AVM arising from the right optic disc was noted; cerebral angiography demonstrated no evidence of orbital or intracranial abnormalities. Episodic severe visual loss, worse at higher altitudes, developed when the patient was 36 years of age; the fundus examination at that time was unchanged. Seven years later, however, persistent visual loss developed and a central retinal vein occlusion was noted. Using fluorescein angiography, the blood supply to the AVM was found to be reduced, and neovascularization later developed. The transient episodes of visual loss described by this patient before the retinal vein occlusion represent uncommon manifestations of retinal AVMs, and are most likely to represent ischemia secondary to "steal" phenomena. Several potential mechanisms for venous occlusions in the setting of this rare entity were implicated, including venous stasis and compression with reduced outflow at the level of the central retinal vein.

In patients with retinal emboli, the aortic arch may represent an underrecognized source. Atheromatous plaques in the aortic arch may be demonstrated by transesophageal echocardiography, as indicated in two recent case reports by Romano et al. (11). Both patients, aged 91 and 67 years, had retinal emboli, the most likely source of which could not be identified by carotid ultrasound, MR angiography, or transthoracic echocardiography. When transesophageal echocardiography was performed, calcified plaques in the aortic arch and ascending aorta were recognized in both patients. The authors (11) suggest that, although the optimal treatment for aortic arch embolic disease has not been defined, transesophageal echocardiography in selected patients may help identify this underemphasized cause of retinal emboli.

Retinal and other neuro-ophthalmologic manifestations of internal carotid artery dissection were reviewed by Biousse and colleagues (12). They evaluated 146 consecutive patients (29 retrospectively, 117 prospectively) who had extracranial internal carotid artery dissection from 1972 to 1997. Ophthalmologic signs and symptoms were frequent in this series. The most common manifestation was a painful Horner's syndrome (present in 65/146, 44%), which was isolated in nearly 50% of cases. Transient monocular visual loss and "scintillations" were also common (41/146, 28%), and were often induced by looking at a bright light. Permanent visual loss caused by ischemic optic neuropathy occurred in four patients. Given the subsequent occurrence of hemispheric stroke in nearly one third of patients in this series who had neuro-ophthalmologic findings, the importance of recognizing internal carotid artery dissection, particularly in
the setting of a painful Horner's syndrome, was emphasized.

### THE OPTIC NERVE

#### Anterior Ischemic Optic Neuropathy

Nonarteritic anterior ischemic optic neuropathy (NAION) is a disorder for which an embolic etiology has been rarely implicated or documented. Whether patients with recent NAION may have higher frequency of ipsilateral emboli in intracranial vessels by transcranial Doppler (TCD) monitoring was investigated by Kosmosky et al. (13). Such an association, according to the authors (13), may provide evidence for a possible embolic mechanism in some patients. TCD was performed on 11 patients with recent (<121 days prior) NAION and 10 age-matched controls. Both (right and left) middle cerebral arteries were monitored for 30 minutes, and the frequency of microemboli in these arteries was recorded. During the TCD monitoring, no microemboli were detected among any of the 11 patients with recent NAION. One control patient, who had a remote history of NAION but also had a prosthetic heart valve, had evidence of emboli (frequency 12/hour). Thus, a recent history of NAION within 4 months before presentation did not appear to be associated with an increased frequency of TCD-detectable microemboli in the middle cerebral arteries.

Anatomic factors, such as the “disc at risk,” are likely contributors to the causation of NAION. Although NAION has been shown to occur most frequently in patients with cupless optic discs, Parsa et al. (14) recently described a patient with sequential (6 years between events) NAION who had generous physiologic optic cups (0.5 cup-to-disc ratio). This 61-year-old man developed typical findings of pallid disc edema and inferior altitudinal field defects during both attacks of NAION. This “exception to the rule” places emphasis on the fact that, despite a strong association with the “disc at risk,” NAION occurs in the absence of this important anatomic risk factor.

Macular edema may also be a feature of NAION. Tombsak and Zalkov (15) examined a series of 12 patients with this finding to determine the visual outcome and fluorescein angiography characteristics. All patients (13 eyes) demonstrated neuro-ophtalmologic findings consistent with NAION, including visual acuity loss, field defects, and disc edema. During an average follow-up period of 5.3 months, improvement in visual acuity occurred in 11/13 eyes (85%), with a mean improvement of 2.3 Snellen lines (range of improvement up to 9 lines). Although this study examined a small number of patients, this report suggests that patients with NAION and macular edema may have a higher probability of visual recovery. As the authors (15) point out, this recovery is likely caused by the resolution of the macular edema. Furthermore, the macular edema associated with NAION was often subtle in this group, suggesting that its presence may often be underrecognized in the acute setting.

#### Giant Cell Arteritis

A common and formidable cause for anterior ischemic optic neuropathy (AION), giant cell arteritis (GCA), is a disorder for which the clinical course and microscopic pathology suggest the possibility of an infectious etiology. Nordborg and colleagues (16) hypothesized that varicella zoster virus (VZV) may be involved in the pathogenesis of GCA, given its tendency to reactivate and to occur in elderly persons. Temporal artery biopsy specimens were obtained from 10 patients with GCA (all women, mean age 76.6 years). Using polymerase chain reaction (PCR) techniques and immunohistochemical analysis, no evidence of VZV was identified in any of the specimens. These findings indicate that VZV is not an immediate causal agent of GCA.

Visual loss and neurologic dysfunction related to postural changes may occur in GCA. Diego and Margo (17) recently reported two patients with biopsy-proven GCA, both of whom described bilateral transient visual loss after bending over or arising from a supine position. The first patient was a 72-year-old man who reported several 2- to 15-minute episodes of painless visual loss (total darkness) in both eyes associated with changes in position. No signs of carotid disease or ocular abnormalities, such as disc swelling, were discovered on examination; the patient’s visual loss was thus attributed to low flow in the verteobasilar circulation. The second patient, also 72 years of age, had bilateral arteritic AION. On the second day of her hospitalization for intravenous steroid therapy, she experienced a 15-minute episode of complete visual loss in both eyes after bending over. The cause in this patient was thought to be insufficiency in the vertebral or ocular circulations. While both patients in this report had other symptoms suggestive of GCA, including headache, jaw claudication, and scalp tenderness, postural vision loss may be an important cause of visual dysfunction in GCA.

Many unusual nonvisual manifestations may also accompany GCA. One such sign is scalp necrosis. In a report of two patients, Dudenheofer et al. (18) emphasized that this valuable sign may be overlooked. Both of their patients had scalp necrosis, characterized by alopecia, crusting, vesicles, edema, and erythema in the distribution of the superficial temporal arteries. In one patient, the visual loss was preceded by scalp necrosis, while in the other, the skin findings were key to establishing the GCA diagnosis.

Vernet’s syndrome, characterized by simultaneous unilateral involvement of cranial nerves IX, X, and XI, is another rare manifestation of GCA. Gout et al. (19) recently described a 73-year-old man who was hospitalized for the sudden onset of dysphagia and dysphonia. He had also developed temporal headache. Examination revealed paralysis of the right palatine velum, right vocal cord paralysis, and weakness of the right sternocleidomastoid. The sedimentation rate was 130 mm/hour. CT and MRI scans of the brain and skull base were normal. Temporal artery biopsy was consistent with GCA. Vernet’s syndrome, rare in the setting of GCA, is thought to be caused by arteritic involvement of external carotid
artery branches, including the ascending pharyngeal artery. In the patient presented by Gout et al. (18), the ascending pharyngeal artery was narrowed on cerebral angiography. The sudden onset of the patient's symptoms and their rapid resolution after steroid therapy also provided evidence for an arteritic etiology.

Optic Neuritis

Important 5-year results from the Optic Neuritis Treatment Trial (ONTT) were reported in late 1998. Cole and colleagues (20) reassessed the predictive value of cerebrospinal fluid (CSF) oligoclonal banding for the development of clinically definite multiple sclerosis (CDMS) within 5 years after monosymptomatic optic neuritis. Among the 457 patients who participated in the ONTT, 76 underwent lumbar puncture and brain MRI within 24 hours of enrollment. The baseline demographic characteristics of this subgroup were similar to those of the entire ONTT cohort, with a mean age of 33 years. During the 5-year follow-up period, 227/76 patients (29%) developed CDMS. Among the 38 patients who had oligoclonal bands in the CSF at the time of the initial attack of optic neuritis, CDMS developed in 16 (positive predictive value = 42%), whereas only 6/38 patients (16%; negative predictive value 84%) without oligoclonal bands developed CDMS. The presence of CSF oligoclonal bands was thus associated with the development of CDMS in this group of patients (odds ratio = 3.88; 95% CI 1.18, 13.86; p = 0.02). However, when the results of the initial brain MRI were also considered, the predictive value of CSF oligoclonal banding was most apparent in the group with no brain lesions on MRI (39 patients). CDMS developed in 3/11 patients (27%) with normal MRI and positive oligoclonal banding, whereas 1 patient of 28 (4%) with normal MRI and no oligoclonal bands developed CDMS (p = 0.06). No such differences were found among those with abnormal MRI scans (one or more brain lesions). As Cole et al. (20) emphasized, CSF oligoclonal banding is a potentially useful predictor of CDMS at 5 years after monosymptomatic optic neuritis. Oligoclonal bands were most helpful in predicting CDMS among those patients for whom the initial brain MRI was normal. Brain MRI therefore continues to be the most powerful predictor of CDMS in patients with monosymptomatic optic neuritis.

Cerebrospinal fluid oligoclonal bands are typically absent in patients with Devic's neuromyelitis optica, a disorder characterized by demyelination of the optic nerves and spinal cord without brain involvement. Because the outcomes of patients with this disease are often poor, Mandler et al. (21) performed an observational pilot trial of steroids and azathioprine treatment in seven patients with newly diagnosed Devic's neuromyelitis optica. All patients were women, ranging in age from 34 to 73 years. Brain MRI scans were normal in all, with the exception of optic nerve involvement. CSF oligoclonal bands were absent in all seven patients. After baseline laboratory testing, all patients were given high-dose intravenous methylprednisolone (500 mg twice daily) for 5 days, followed by oral prednisone at 1 mg/kg per day for 2 months. This was followed by a slow taper to a maintenance dose of 10 mg/day. Three weeks after the start of steroid therapy, oral azathioprine was begun at a dose of 2 mg/kg per day, with the goal of a maintenance dose of 75 to 100 mg per day. Expanded Disability Status Scale (EDSS) scores demonstrated significant improvement from baseline (mean score 8.2; severe disability) at 6 months (mean 6.6, p < 0.001), 12 months (mean 5.0, p < 0.0001), and 18 months (mean 4.0, p < 0.0001). The mean EDSS score at 18 months (4.0, range 3.0–6.0) indicated that, by that time, most patients could ambulate without assistance. This pilot trial, although observational, provides preliminary evidence that prednisone and azathioprine therapy may provide safe and effective treatment for patients with newly diagnosed Devic's neuromyelitis optica. However, larger randomized trials are needed to address this question and to further evaluate the prevalence of side-effects.

Infectious, Inflammatory, and Postsurgical Optic Neuropathies

Unusual presentations of infectious and inflammatory optic neuropathies continue to be reported in the neuro-ophthalmologic literature. Mansour (22) recently described a 29-year-old patient with a rare finding of an optic disc tube. The patient had blurred vision in both eyes of several weeks' duration. Examination revealed granulomatous iritis and bilateral optic disc edema. The left optic disc, however, was severely swollen, with a large nodular evaluation at the nasal border. A nodule was likewise present on chest radiography, and the purified protein derivative (PPD) test was positive for tuberculosis. The patient's visual symptoms resolved with antituberculous therapy (isoniazid, ethambutol, rifampin), although the peripapillary granuloma in the left eye persisted. Mansour (22) emphasized the uncommon nature of disc edema and optic disc tubercles as presenting features of tuberculosis, and stressed that tuberculosis must always be included on the list of potential causes for infiltrative optic neuropathy.

An unusual case of hypertrophic cranial pachymeningitis and optic neuropathy caused by Pseudomonas aeruginosa was described by Girkin et al. (23). A 60-year-old man developed multiple progressive cranial neuropathies manifested by hoarseness, dysphagia, decreased hearing, facial weakness, and diplopia. The initial lumbar puncture and MRI were unrevealing. Six months later, he had ptoxis, ophthalmoparesis, and loss of vision in the right eye to no light perception. Diffuse dural thickening and enhancement were noted on MRI, particularly at the right sphenoid ridge, clivus, petrous apex, and cavernous sinus. Subfrontal biopsy revealed the dura with granulomatous inflammation and intracellular gram negative bacteria. Cultures grew P. aeruginosa. The patient was treated with tobramycin and cefazidine with marked improvement of the cranial neuropathies. This report and comprehensive review by Girkin et al. (23) serves as a reminder of the many potential causes of cranial and optic neuropathies. In the case of hypertrophic cranial pachymeningitis, a search
for an underlying infectious cause must be undertaken so that appropriate therapy may be initiated.

Forman and Rosenbaum (24) presented the clinical, biopsy, and autopsy findings for a patient who had isolated optic neuropathy as the presenting feature of lymphomatoid granulomatosis. This 41-year-old woman was seen initially for a 1-week history of visual loss and pain on eye movement. Examination revealed a visual acuity of 20/100 in the affected left eye; color vision loss, an afferent papillary defect, and optic disc edema were noted. The visual loss progressed to no light perception in the left eye. A lung biopsy, performed to evaluate progressive dyspnea and pulmonary infiltrates, was consistent with lymphomatoid granulomatosis, demonstrating atypical lymphoid cells that were immunopositive for T-cell markers. After the patient’s death as a result of respiratory failure, a cross section of the optic nerve revealed infiltration by atypical lymphocytes with pleomorphic nuclei, again immunopositive for T-cell markers. This unusual neuro-ophthalmologic presentation of lymphomatoid granulomatosis was initially consistent with typical idiopathic optic neuritis. In such patients, the continued progression of visual loss or other atypical characteristics should prompt investigation for systemic disorders that may cause inflammatory optic neuropathies.

A more benign form of optic disc edema, which may occur after trabeculectomy, was discussed by Kawasaki and Purvin (25) in a report of two patients. The first patient, a 24-year-old woman, was found to have asymptomatic optic disc edema 2 weeks after trabeculectomy for glaucoma. The edema persisted for 4 months despite intraocular pressures that were no lower than 7 to 14 mmHg. She reported a 10-month history of headache and pulsatile tinnitus; her medical history was remarkable for obesity. Examination revealed unilateral optic disc edema and enlargement of the blind spot on visual field testing. MRI was normal and CSF opening pressure was 250 mm water. The disc edema resolved with observation and weight loss. The second patient, a 51-year-old moderately overweight woman (207 pounds), developed similar unilateral optic disc edema with blind spot enlargement. Her CSF opening pressures were likewise mildly elevated at 195 to 210 mm water, and, retrospectively, she had been experiencing transient visual obscurations. The authors (25) propose that relative decreases in intraocular pressure to the low-normal range in these patients, along with high-normal intracranial pressures, may have precipitated the development of optic disc edema. Because the development of optic disc edema after trabeculectomy likely depends on the relative difference in intracranial versus intraocular pressure, severe ocular hypertension may not be required for disc edema to manifest in patients with mildly elevated intracranial pressure.

Meningiomas and Other Neoplasms

Anterior visual pathway meningiomas account for as many as 10% of all primary orbital tumors, as recently emphasized by Stafford et al. (26). They reviewed the records of 581 consecutive patients at the Mayo Clinic, Rochester, NY, who underwent resection for primary meningiomas from 1978 to 1988. Their search revealed 43 patients with anterior visual pathway meningiomas, involving the intraorbital or intracranial portions of the optic nerve. Records were reviewed for completeness of surgical resection (gross total vs. subtotal), evidence of radiographic recurrence, treatment after recurrence, histopathologic features, and demographic characteristics. The group of 43 patients with resected anterior visual pathway meningiomas was compared to those who had undergone resection for nonanterior visual pathway meningiomas (528 patients) to determine whether certain factors may be associated with tumor recurrence. The anterior visual pathway group was significantly younger at diagnosis, with a median age of 47 years (vs. 58 years in the nonanterior visual pathway group, p = 0.001). As may have been expected based on tumor location, a significantly greater proportion of the anterior visual pathway group had subtotal resections (60% vs. 17%, p = 0.001). Recurrence-free survival in the anterior visual pathway group was significantly less than in the nonanterior visual pathway group (p < 0.001, Kaplan-Meier method); the relative risk of recurrence in the anterior visual pathway group was 3.4 (95% CI 2.1–5.3) over a median follow-up of 8.3 years. At 5 years, recurrence-free survival in the anterior visual pathway group was 62% (95% CI 49–70%) vs. 85% to 90% in the nonanterior visual pathway group. As the authors (26) point out, the lower recurrence-free survival in the anterior visual pathway group is likely related to factors other than subtotal resection alone, such as tumor site within the anterior visual pathway, male sex, age younger than 40 years, and increased numbers of mitotic figures (multivariate analysis). Although surgical resection remains the treatment modality in patients with symptomatic meningiomas of the anterior visual pathway, radiation therapy is recommended in the setting of optic nerve sheath or cavernous sinus involvement (26), for which the potential morbidity of surgical resection is great.

POEMS syndrome (polyneuropathy [P], organomegaly [O], endocrinopathy [E], monoclonal gammopathy [M], and skin changes [S]) may be associated with optic disc swelling. Wong and colleagues (27) presented a 25-year-old woman who developed episodic horizontal diplopia, metamorphopsia, and positive visual phenomena. Initial examination revealed visual acuities of 20/25 in both eyes and a left abduction deficit. Two months later, she was noted to have bilateral optic disc swelling and blind spot enlargement. Brain CT and spinal fluid opening pressure were normal. The patient was later found to have osteolytic bone lesions secondary to multiple myeloma. She died from multiorgan failure and hepatic venous blockage after an autologous bone marrow transplant. This patient met criteria for POEMS syndrome, with a progressive demyelinating polyneuropathy, hepatomegaly, hypothyroidism, monoclonal gammopathy, and skin hyperpigmentation. Unusual features in this patient, as pointed out by the authors (27), included young age, female sex (older males are most typically affected), and the presence of osteolytic (rather than osteosclerotic)
bone lesions. Neuro-ophtalmologists should be alerted to this unusual cause of optic disc swelling, which may be related to cytokine-mediated changes in vascular permeability at the optic nerve head.

Another uncommon cause of visual dysfunction that must be considered in the setting of bilateral, unexplained visual loss is paraneoplastic optic neuropathy. Luiz et al. (28) described one such patient whose underlying malignancy was small cell carcinoma of the lung. This 59-year-old woman developed acute, painless, bilateral visual loss accompanied by headaches and difficulty walking. Visual acuities were 20/30 in the right eye and 20/40 in the left; examination was notable for keratic precipitates, vitreous cells, severely constricted visual fields, and bilateral optic disc edema. Horizontal jerk nystagmus, dysarthria, and ataxia were also present. MRI of the brain was normal; however, CT scans of the chest demonstrated mediastinal, paratracheal, and hilar adenopathy. Lumbar puncture revealed a lymphocytic pleocytosis (122 WBC) and elevated protein (111 mg/dl). Small cell lung carcinoma was demonstrated by mediastinoscopic biopsy because no masses were detected in the lungs. Serum autoantibodies were demonstrated against a 60 kd protein, which is present in optic nerve, cerebral cortex, and cerebellum. Anti-Hu, anti-Yo, anti-Ri, and CAR antibodies were negative. ERG was normal, although a focal ERG was not performed. A diagnosis of paraneoplastic optic neuropathy and cerebellar syndrome was made. The visual loss and ataxia improved with corticosteroid treatment and chemotherapy.

**Idiopathic Intracranial Hypertension**

The pathophysiologic mechanisms that underlie the development of idiopathic intracranial hypertension (IIH) remain unknown. Leker and Steiner (29) found a high prevalence of anticytodiin antibodies in a group of 14 patients with IIH. These patients were evaluated in Jerusalem, Israel, from 1989 to 1995. All patients in the analysis had normal MRI, normal MR venography or conventional angiography, and CSF opening pressures above 250 mm water. Five additional patients with IIH had been excluded because of inadequate neuromaging or minor abnormalities, such as an empty sella. The mean age in the group of 14 patients with IIH was 25.9 years (range 13–42); 12 patients (86%) were female. Anticytodiin antibodies were detected in the serum of 6/14 patients (43%) on at least two occasions. A high prevalence of anticytodiin antibodies was found in this small group of patients with IIH. The direct implications of this finding in the pathogenesis of IIH remain unclear. Although the authors (29) suggest screening for anticytodiin antibody in patients with IIH, they are also correct in emphasizing the need for future studies in which larger groups of consecutive patients are examined.

Minocycline and other tetracycline antibiotics have also been implicated in the etiology of IIH. Although neither causation nor definite association have been demonstrated in large case-control studies, reports describing the development of IIH after the initiation of minocycline treatment have continued to emerge. Chiu et al. (30) reviewed the records of 12 patients with IIH who had been treated recently with minocycline for refractory acne vulgaris. These patients, from five neuro-ophtalmic referral centers, had a median age of 26.5 years (range 13–40); 33% were obese. Symptoms of IIH had developed within 2 months of the start of minocycline treatment in 9/12 patients (75%). The authors (30) state, based on the findings of this observational study, that minocycline is a cause or precipitating factor in the development of IIH. However, we agree that efforts to examine this potential association must continue in the form of large, multicenter studies of risk factors for IIH. A history of minocycline use should be sought in all patients with a new diagnosis of IIH.

Magnetic resonance imaging is an important tool in the diagnostic evaluation of IIH. Brodsky and Vaphiades (31) investigated whether the presence of certain findings of MRI could provide evidence for elevated intracranial pressure in patients with suspected IIH. They reviewed MR images of the brain and orbits for 20 patients with IIH and 20 age-matched controls. The following findings were detected in a higher proportion of patients with IIH versus controls: 1) flattening of the posterior sclera (80% IIH vs. 5% controls), 2) empty sella (70% vs. 5%), 3) distension of the peripapillary subarachnoid space (45% vs. 5%), 4) enhancement of the prelaminar optic nerve (50% vs. 0%), 5) vertical tortuosity of the orbital optic nerve (40% vs. 5%), and 6) intracranial protrusion of the prelaminar optic nerve (30% vs. 5%). These findings are demonstrated in Figure 2; all were present at least once in IIH patients but did not necessarily coexist. IIH.

Obesity and weight gain are known risk factors for IIH. Johnson and colleagues (32) investigated whether weight loss, in conjunction with acetazolamide therapy, could be associated with a more rapid resolution of papilledema in patients with IIH. They reviewed the records of 48 consecutive patients with IIH; 15 met criteria for this study, including initial neuro-ophtalmologic examination within 10 days of diagnosis, initial treatment with acetazolamide and weight loss only, a single lumbar puncture performed at diagnosis, stereoscopic optic disc photographs obtained at diagnosis and during follow-up, and weight measurements obtained at initial examination and throughout the 24-week follow-up period. The mean weight at initial examination for the 15 patients was 110.5 kg, with a mean body mass index of 40.7 kg/m². Using the Frisen classification, it was determined that 11 patients (73.3%) had improvement of papilledema during follow-up, with complete resolution over a median period of 8.5 weeks in 10 patients (66.7%). The degree of weight loss observed in patients whose papilledema resolved by one Frisen grade was 3.3%, while a 6.6% weight loss was seen in those who had improvement by three Frisen grades (corresponding to complete resolution of marked papilledema). Of the four patients who...

took acetazolamide but did not experience weight loss during follow-up, none had improvement of papilledema. Percent weight loss was significantly correlated with papilledema grade change ($r_c = 0.73$, $p = 0.002$). In addition to improvement of papilledema in 11/15 patients, 13 patients had stabilization or improvement of visual acuity to 20/20 or better during follow-up. Larger investigations, incorporating papilledema and other indicators of visual outcome and natural history data, will be needed to confirm these findings. Until then, weight loss remains a valuable treatment modality for IIH.

**Leber’s Hereditary Optic Neuropathy**

In response to the observation of other investigators that the pupillary light reflex may remain intact in patients with Leber’s hereditary optic neuropathy (LHON),
Jacobson et al. (33) retrospectively examined a cohort of patients with LHON and monocular visual loss to evaluate this issue. The neuro-ophthalmologic examination records of 10 patients with LHON and monocular visual loss were reviewed. All patients had undergone pupillary examinations with quantification of the afferent pupillary defect (APD) using neutral density filters. For each patient, the magnitude of the APD was compared with the magnitude of the APD that would have been predicted based on the degree of visual loss documented by automated (eight patients) or Goldmann (two patients) perimetry. APDs were detected in all patients, ranging in magnitude from 0.3 to 1.8 log units (median 0.9 log units). The median predicted APD magnitude was 0.9 log units, and there was no significant difference in magnitude between the measured and predicted APDs ($p = 0.13$). Therefore, contrary to prior observations, this study did not demonstrate that pupillary light reactions are relatively spared in patients with LHON.

**THE OPTIC CHIASM AND BEYOND**

**Pituitary Adenomas**

Pituitary adenomas, common tumors in adult patients, occur infrequently in children. The clinical characteristics of 10 pediatric patients with pituitary adenomas were recently reviewed by Lee et al. (34). These children, aged 2 to 16 years (median 4 years), were seen at two neuro-ophthalmic referral centers from 1989 to 1996. Visual loss was present in five patients (50%) at diagnosis, with visual acuities ranging from 20/20 to 20/200 in the better eyes, and 20/100 to light perception in the worse eyes. Temporal and bitemporal field defects were present in four of five patients with visual loss. Three patients experienced visual improvement after surgery. Of the five children with visual loss, four were adolescents ranging in age from 12 to 15 years. The two youngest children in the group, aged 2 and 7 years, did not have visual loss but had accelerated growth and precocious puberty. Lee and colleagues (34) noted that the pediatric patients included in this study seemed to have severe visual loss, perhaps more severe than that initially seen in adult patients. Further studies, with direct comparisons between adult and pediatric patient populations with pituitary adenomas, are necessary to confirm this observation.

**See-Saw Nystagmus**

See-saw nystagmus may be a presenting feature of tumors and other mass lesions in the parasellar region. Dell’Osso and Daroff (35) recently described "Two Additional Scenarios for See-Saw Nystagmus": achiasma and hemichiasma. Achiasma, a congenital absence of the optic chiasm, precludes the development of binocular vision. As reported by the authors (35), achiasma has been associated with see-saw nystagmus not only in canine models, but also in humans (four individuals have been identified to date). Such patients demonstrate abnormalities on visual evoked potential testing and MRI. Although hemichiasma, or unilateral failure of retinal fiber decussation, has not yet been described in humans, the authors (35) suggest considering achiasma and hemichiasma in infants and young children with see-saw nystagmus.

**Band Optic Atrophy**

Band, or “bow-tie,” optic atrophy is most commonly associated with lesions of the contralateral optic tract. A variable degree of temporal disc pallor is also noted in the eye ipsilateral to the optic tract lesion. Band optic atrophy may also be present unilaterally in the setting of congenital abnormalities, as demonstrated in a report by Turbin et al. (36). They presented an 11-year-old boy who had findings of band optic atrophy in the left eye and an ipsilateral dense temporal hemianopic defect. The right eye funduscopic examination and visual field were normal, with a visual acuity of 20/20. The left eye visual acuity was reduced to 20/200, attributed in part to strabismic amblyopia (the patient had a large angle exotropia for at least 3 years before examination). An MRI scan of the brain revealed atrophy of the left optic nerve from the globe to the chiasm and an area of left cortical gray matter heterotopia. No evidence of an optic tract lesion was noted. The authors (36) suggest that the unilateral band optic atrophy that occurred in this unique patient may relate to neuronal migration abnormalities similar to those responsible for the ipsilateral cortical heterotopia. However, band atrophy may result from any anterior visual pathway lesion associated with a temporal hemianopic defect.

**Sellar Arachnoid Cysts**

Arachnoid cysts arising in the parasellar region may be confused with cysts of the pituitary, and may represent a rare cause of visual loss secondary to optic chiasm or tract involvement. Chun et al. (37) presented two such patients. The first was a 33-year-old woman who had diplopia and painless, progressive visual loss in 1987. Decompression of a suprasellar arachnoid cyst produced improvement in her vision. Nine years later, her vision again worsened, and an incongruous left homonymous hemianopsia was noted. MRI revealed a suprasellar arachnoid cyst compressing the right optic tract and chiasm. Fenestration of the cyst and placement of an Omaya shunt resulted in visual improvement. The second patient, a 64-year-old man with a history of headaches, was found to have a bitemporal hemianopsia on a routine ophthalmologic examination. Upward displacement of the optic chiasm by a sellar arachnoid cyst was demonstrated by the initial MRI scan. However, repeat MRI performed after the visual field defects had been observed to spontaneously resolve, showed resolution of the mass effect, likely secondary to spontaneous decompression. The authors (37) point out that the most typical neuro-ophthalmologic finding in patients with suprasellar arachnoid cysts is bitemporal hemianopsia. This unusual entity should be added to the list of possible etiologies for compressive lesions involving the optic chiasm and, even more uncommonly, the optic tracts.

**Traumatic Lateral Geniculate Hemorrhage**

"Why Fighting Makes You See Black Holes Instead of Stars" was the topic of a report by Kosmosky and Lan-
cione (38) of a boxer who developed a traumatic lateral geniculate hemorrhage. One month after a knockdown by his opponent, this 19-year-old was evaluated for visual loss in his left hemifield. The visual symptoms had been noted by the patient immediately after the injury. Examination revealed an incongruous left homonymous hemianopsia; visual acuities were 20/20 and there was no afferent pupillary defect. T2-weighted MR images showed an area of encephalomalacia in the region of the right lateral geniculate nucleus; this area was thought to be consistent with a previous hemorrhage. Trauma is thus a rare but possible cause of lateral geniculate hemorrhage and homonymous hemianopsia.

REFERENCES

To the Editor:

Turbin et al. (1) reported an 11-year-old boy with decreased visual acuity, a left afferent pupillary defect, temporal hemianopic visual field loss in the left eye only, and monocular band optic atrophy. The authors described the possible topographic localization for a lesion causing such findings.

H. M. Traquair previously had used the term “junction scotoma” to refer to a monocular temporal hemicentral field defect caused by compression of the nasal fibers crossing at the junction of the intracranial optic nerve and optic chiasm. Miller has emphasized that this junction scotoma is different from the more commonly used term, “junctional scotoma” (an ipsilateral optic neuropathy and a contralateral superotemporal defect). To differentiate these two junctional visual field defects, J. Lawton Smith proposed that the strictly unilateral temporal visual field defect described by Traquair be called the “junctional scotoma of Traquair” to distinguish this defect from the contralateral superotemporal defect referred to as the junctional scotoma (2).

I wonder if the authors could comment on whether their findings represent a noncompressive junctional scotoma of Traquair. Perhaps the authors have added a newly recognized (or at least underemphasized) finding (monocular band atrophy) to the criteria for this type of junctional visual field loss. I, for one, will be looking more closely at the type of atrophy in the optic nerve in future cases of monocular hemianopic visual field loss.

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REFERENCES
Announcements

NANOS Young Investigator Award

At the 25th annual meeting of The North American Neuro-Ophthalmology Society, the award was presented to Wolf Lagreze, MD, of Freiburg, Germany, for "Neuroprotection with Memantine, Cerestat, and Riluzole in a Rat Model of Acute Retinal Ischemia."

NANOS Resident/Fellow Award

At the 25th annual meeting of The North American Neuro-Ophthalmology Society, the award was given to John Kerrison, MD, for "Congenital Motor Nystagmus Linked to Xq26-q27."