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CALENDAR
Non-Arteritic Anterior Ischemic Optic Neuropathy, Erectile Dysfunction Drugs, and Amiodarone: Is There a Relationship?

Frederick W. Fraunfelder, MD, and Thomas Shults, MD

Two articles have appeared recently in this journal on the subject of erectile dysfunction drugs and non-arteritic ischemic optic neuropathy (NAION) (1,2). The first article (1) reported seven new cases of NAION in patients who had used sildenafil (Viagra®) shortly before developing NAION. The second report (2) represented the view of Sohan Singh Hayreh, MD, an acknowledged expert on ocular blood flow and NAION, that there is sufficient evidence to support a cause-and-effect relationship between the use of erectile dysfunction drugs and the development of NAION. Another viewpoint article published last year in this journal (3) reviewed the subject of amiodarone and NAION, concluding that a cause-and-effect relationship seemed unlikely but could not be excluded.

These papers epitomize the dilemma confronting clinical toxicologists, especially in ophthalmology. In this subspecialty, sufficient funding is rarely available for adequate toxicological research once a drug has been approved for clinical use. For the most part, clinical ocular toxicology consists of a series of published case reports or reports to The National Registry of Drug-Induced Ocular Side Effects.*

This registry acts as a repository of spontaneous case reports and attempts to give the clinician guidance as to drug-related adverse effects on the visual system by analyzing the data and reporting the results when necessary (4,5). The case reports are usually received from treating ophthalmologists who suspect an adverse drug reaction from an eye drop or an ocular reaction from a systemic medication. Many reports are received over the telephone and documented as such. Data garnered from these spontaneous reports are sometimes premature, of poor quality, incomplete, or suffer from poor follow-up. Even so, spontaneous reports from clinicians can be the first signal that an adverse ocular reaction from a medication exists.

The problem of determining causation of NAION by erectile dysfunction drugs or amiodarone is made especially difficult because NAION is a relatively rare event with poor numerator/denominator data and the NAION associated with the use of these agents appears to have few if any manifestations that distinguish it from spontaneously-occurring NAION.

How does a clinical ocular toxicologist evaluate a potentially causal relationship between the use of a pharmacologic agent and a medical condition that arises in its users? We depend on seven criteria (Table 1): 1) a close temporal association between use of the agent and the appearance of the condition; 2) a dose-response relationship to the likelihood of the occurrence of the condition; 3) positive de-challenge evidence; 4) positive re-challenge evidence; 5) a plausible causal mechanism for the agent; 6) a “class effect,” that is, evidence that other agents of similar type and action have also been implicated; and

*Casey Eye Institute, 3375 SW Terwilliger Boulevard, Portland, OR 97239-4197; (503) 494-4318; www.eyedrugregistry.com
Casey Eye Institute (FWF), Oregon Health & Science University, and Legacy Good Samaritan Devers Memorial Eye Clinic (TS), Portland, Oregon.
Address correspondence to F.T. Fraunfelder, MD, Casey Eye Institute, 3375 Southwest Terwilliger Boulevard, Portland, OR 97239-4197; E-mail: eyedrug@ohsu.edu
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TABLE 1. The seven criteria used to suspect a drug-induced adverse effect

1. There is a temporal association (side effect occurs within a reasonable amount of time from drug administration)
2. There is a dose-response relationship (the frequency or intensity of the unwanted effect is correlated with increasing drug dose)
3. There are positive de-challenge data (when use of the drug stops, the unwanted effect ceases or improves)
4. There are positive re-challenge data (after positive de-challenge, the unwanted effect occurs in the same pattern as it did upon original use of the drug)
5. There is a plausible scientific explanation for a mechanism of action that could cause the unwanted effect
6. Similar unwanted effects occur from other drugs in the same class
7. There is no alternative explanation for the unwanted effect

7) lack of a plausible alternative explanation. Amalgamation of the evidence within these seven criteria leads to a grading of likelihood of a cause-and-effect relationship based on World Health Organization (WHO) standards (Table 2).

Do erectile dysfunction drugs cause NAION? Here are the data:
1. Temporal association: In the approximately 25 published (1,6-13) and unpublished (14) cases of NAION, many do not fall within the plasma half-life of 4 hours for sildenafil and vardenafil or 30 hours for tadalafil (15). Recovery times are within the range of spontaneously-occurring NAION.
2. Dose response: There are not enough data to evaluate this criterion.
3. Positive de-challenge: Data are incomplete, but when the drug has been stopped, the clinical course appears to be no different from that of spontaneously-occurring NAION.
4. Positive re-challenge: A single, well-documented case (8) showed compelling evidence for positive re-challenge in a patient using tadalafil.
5. Plausible mechanism of action: Hayreh (2) has described various mechanisms that could account for causation of NAION by erectile dysfunction drugs based on their physiologic properties, but no mechanism has been proven.
6. Similar effect from other drugs in this class: All three erectile dysfunction drugs appear to cause the same visual effects (16). If one of these drugs can cause NAION, then in all probability, all three will.
7. No alternative explanation: The incidence of NAION is low and the exposed population is very large (sildenafil alone has more than 23 million habitual users/year). The exposed population is largely in the age group and risk factor group for spontaneous NAION.

Based on these data, the association between erectile dysfunction drugs and NAION is possible based on WHO criteria, a conclusion affirmed in prior reports (15,16). This WHO classification may change as additional data become available.

We concur with the new FDA recommendations regarding the use of erectile dysfunction drugs (17):
"Physicians should advise patients to stop use of all PDE-5 inhibitors, including sildenafil, and seek medical care immediately if they develop blurred or cloudy vision in one or both eyes.

TABLE 2. World Health Organization definitions: Causality assessment of suspected adverse reactions

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Certain</td>
<td>A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and that cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary.</td>
</tr>
<tr>
<td>Probable/likely</td>
<td>A clinical event, including laboratory test abnormality, occurring within a reasonable time sequence from administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and following a clinically reasonable response on withdrawal (de-challenges). Re-challenge information is not required to fulfill this definition.</td>
</tr>
<tr>
<td>Possible</td>
<td>A clinical event, including a laboratory test abnormality, occurring within a reasonable time sequence from administration of the drug, but one that could also be explained by concurrent disease or the presence of other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.</td>
</tr>
<tr>
<td>Unlikely</td>
<td>A clinical event, including a laboratory test abnormality, with a temporal relationship to drug administration that makes a causal relationship improbable and for which other drugs, chemicals, or underlying disease provide plausible explanations.</td>
</tr>
<tr>
<td>Conditional unclassified</td>
<td>A clinical event, including a laboratory test abnormality, reported as an adverse reaction, about which more data are essential for a proper assessment or the additional data are under examination.</td>
</tr>
<tr>
<td>Unassessible/unclassifiable</td>
<td>A report suggesting an adverse reaction that cannot be judged because information is insufficient or contradictory, and that cannot be supplemented or verified.</td>
</tr>
</tbody>
</table>
attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, that has been reported rarely post-marketing in temporal association with the use of all PDE-5 inhibitors. It is not possible to determine whether these events are related directly to the use of PDE-5 inhibitors or to other factors.

Physicians should also discuss with patients the increased risk of NAION in individuals who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators such as PDE-5 inhibitors.”

We do not believe that current evidence supports a practice of screening actual or potential erectile dysfunction drug users for a small cup-to-disc ratio, a feature said to predispose to spontaneous NAION, nor do we support the suggestion that informed consent is necessary for the prescription of these drugs.

Does amiodarone cause NAION? Here are the data:
1. Temporal association: The duration of drug exposure has varied widely.
2. Dose response: There are no data.
3. Positive de-challenge: Some patients improve, but most do not.
4. Positive re-challenge: There are no data. In fact, in some patients, vision improves despite continued use of the drug.
5. Scientific explanation as to mechanism of action: None is proven.
6. No alternative explanation: Most cases of NAION arise in patients at risk for spontaneously-occurring NAION.

Thus, amiodarone rises no higher than a possible cause of NAION albeit that several recent trial outcomes suggest that juries are convinced of a more solid link. As Murphy and Murphy (3) have stated in their thoughtful review, “it is unclear whether the optic neuropathy is due to toxic effect of the drug, whether it is simply a variant of NAION in which resolution of disc swelling is prolonged, or whether it is an independent risk factor for NAION.”

However, unlike the selective PDE-5 inhibitors used for erectile dysfunction, whose use can be avoided without adverse physical (if not emotional) consequence, amiodarone is often deemed potentially life-saving for patients with cardiac arrhythmias. Accordingly, an across-the-board dictate to avoid its use in patients who have vasculopathic or possible anatomic risk factors for NAION will cause more harm than good. The evidence supporting the benefit of amiodarone is far more solid than the evidence of its causing NAION.

The decision to discontinue amiodarone rests with the cardiologist. The role of the ophthalmologist and neuroophthalmologist is advisory and perhaps educational. Cardiologists should be made aware that the causal association between amiodarone use and NAION cannot be entirely excluded. If the indication for amiodarone is not compelling, and there are alternative effective drugs without an association with NAION, then such agents might be considered in patients with arteriosclerotic risk factors and cupless optic discs.

REFERENCES
17.2552-6.
Third, Fourth, and Sixth Cranial Nerve Palsies Following Closed Head Injury

Avninder Dhaliwal, MD, Adrienne L. West, MD, Jonathan D. Trobe, MD, and David C. Musch, PhD

Background: The relationship between the circumstances and severity of closed head injury (CHI) and the clinical and imaging features of cranial nerve 3, 4, and 6 palsies has not been rigorously addressed in a large study.

Methods: Retrospective chart review of 210 consecutive patients with CHI examined at a single tertiary care center from 1987 to 2002. Patients were located by searching the ophthalmology inpatient consultation and neuro-ophthalmology outpatient databases and hospital emergency room billing codes for a diagnosis of traumatic 3, 4, or 6 cranial nerve palsy (Cranial Nerve Injury Group) and a diagnosis of CHI without traumatic 3, 4, or 6 nerve palsy (Control Group). The Cranial Nerve Injury Group was then subdivided into two groups: those with injuries to an individual cranial nerve and those with multiple (including bilateral) cranial nerve injuries. Comparisons between groups were based on age, gender, type of accident, Glasgow Coma Scale (GCS), documented loss of consciousness (LOC), type of ocular injury, presence of systemic injury, need for rehabilitation, physical therapy and cognitive scores, and imaging features.

Results: The Cranial Nerve Injury Group had a significantly higher severity of head injury, more CT abnormalities, and worse short-term neurologic outcomes as compared with the Control Group. These trends were also found when each cranial nerve injury subgroup was compared with the Control Group. Those with cranial nerve 3 palsy had the most severe head injury; those with cranial nerve 4 palsy had an intermediate level of head injury; and those with cranial nerve 6 palsy had the lowest level of head injury. There were no consistent associations between the location of the imaging abnormalities and which cranial nerve was damaged.

Conclusions: CHI with palsy of an ocular motor nerve was more severe than CHI without ocular motor nerve palsy, as measured by the GCS, intracranial and skull imaging abnormalities, and a greater frequency of inpatient rehabilitation. Palsy of cranial nerve 3 was associated with relatively more severe CHI than was palsy of cranial nerves 4 or 6. The location of the imaging abnormalities did not correlate with a particular cranial nerve injury.

(J Neuro-Ophthalmol 2006;26: 4-10)

Damage to cranial nerves 3, 4, and 6 is a common accompaniment of closed head injury (CHI) in adults (1-3) and children (4,5). The relationship between damage to these ocular motor nerves and other clinical manifestations and imaging abnormalities is not well known, largely because previous reports have been limited to individual cases or small series. In these studies, there is sparse information about imaging and no information about neurological outcomes.

In a retrospective chart review of 210 cases, we gathered information about the nature of the head injury, neuro-ophtalmic features, pertinent imaging findings, physical medicine assessment, and clinical outcome. Our aim was to determine if there were any features of CHI that predicted whether there would be ocular motor nerve damage, and if so, whether these features would predict which ocular motor nerve(s) would be damaged. Finally, we sought to determine if the presence of ocular motor nerve damage predicted neurological outcome.

METHODS

Patient Accrual

After obtaining approval from the institutional review board, we performed a retrospective review of 210 consecutive charts of patients examined between 1987 and 2002 in the neuro-ophthalmology outpatient clinics, inpatient consultation unit, and emergency department of the University of Michigan Medical Center. Patients were located by searching the database of patients seen in the...
outpatient neuro-ophtalmology clinics and ophthalmology inpatient consultation service with a diagnosis of CHI and traumatic ocular motor palsy, as well as the hospital billing codes for patients examined in the emergency room with a diagnosis of CHI.

The CHI patients were then subdivided into those who had a diagnosis of cranial nerve 3, 4, or 6 palsy (Cranial Nerve Injury Group) and those who did not (Control Group). The Control Group was drawn entirely from patients examined in the emergency room.

The Cranial Nerve Injury Group was divided into four subgroups, three with injuries to a single cranial nerve (Cranial Nerve 3 Injury Subgroup, Cranial Nerve 4 Injury Subgroup, and Cranial Nerve 6 Injury Subgroup), and one with multiple (including bilateral) cranial nerve injuries (Multiple Cranial Nerve Injury Subgroup). We compared the Cranial Nerve Injury Group as a whole to the Control Group and each of the four cranial nerve injury subgroups to the Control Group. Then we compared the four cranial nerve injury subgroups to each other. Because the Control Group had a significantly greater number of patients with a fall as the cause of the accident, patients with this mode of injury were excluded from the evaluation to remove bias.

We examined the following variables: age, gender, type of accident, Glasgow Coma Scale (GCS), documented loss of consciousness (LOC), type of ocular injury, presence of systemic injury, need for rehabilitation, physical therapy and cognitive scores, and imaging features.

**Statistical Analysis**

Pearson's $\chi^2$ test or Fisher exact test was used to compare proportions between the Cranial Nerve Injury Group and the Control Group. Contingency table analysis using $2 \times 4$ $\chi^2$ tests was used for comparison of the relative frequencies between the four subgroups. All $P$ values less than 0.15 in the four-way comparisons were then evaluated using Pearson's $\chi^2$ test to evaluate differences between each pair within the four subgroups. Analysis of variance and the Student $t$ test was used for comparison of means. A $P$ value of less than 0.05 was deemed statistically significant, except in the multiple comparisons of imaging results in individual cranial nerve injury groups and controls, wherein Bonferroni's adjustment was used.

**RESULTS**

**Cranial Nerve Injury Group versus Control Group**

The Cranial Nerve Injury Group had a significantly lower GCS than did the Control Group (Table 1). The Cranial Nerve Injury Group also had a higher rate of ocular adnexal, optic nerve, and chest injuries. On imaging, the Cranial Nerve Injury Group more often had manifestations of intracranial injury (particularly in the frontal, temporal, parietal, and interpeduncular regions) and more frequent craniofacial fractures. Craniofacial fractures were present in 46 (49%) of 93 patients in the Cranial Nerve Injury Group but only in 9 (13%) of 71 patients in the Control Group. Intracranial injury was present in 62 (67%) of 93 patients in the Cranial Nerve Injury Group but only in 3 (4%) of 71 patients in the Control Group.

**Cranial Nerve Injury Subgroups versus Control Group**

When the cranial nerve injury subgroups were compared individually to the control group, each subgroup was associated with a higher degree of severity of injury as measured by a lower GCS, a greater frequency of intracranial and craniofacial imaging abnormalities, and a more frequent need for inpatient rehabilitation (Table 2).

**Four-Way Comparison of Cranial Nerve Injury Subgroups**

**Cranial Nerve 3.** Damage to cranial nerve 3 alone was associated with a relatively low GCS, particularly as compared with damage to cranial nerve 6 or to multiple cranial nerves. The subgroup with cranial nerve 3 injury also had higher (worse) physical therapy scores for gait and bed mobility as compared with all other subgroups. Cranial nerve 3-injured patients were also more likely to have been involved in a motor vehicle accident and to have had temporal lobe region imaging abnormalities (Table 3).

**Cranial Nerve 4.** Injury to cranial nerve 4 appeared to be of intermediate severity between injury to cranial nerves 3 and 6, but not significantly different from other subgroup, as judged by the GCS.

**Cranial Nerve 6.** Injury to cranial nerve 6 was significantly less severe than to cranial nerve 3, but not significantly less severe than injury to cranial nerve 4, as measured by the GCS. Patients with cranial nerve 6 injury required significantly less frequent inpatient rehabilitation than all other subgroups.

**Multiple Cranial Nerves.** Patients with multiple cranial nerve injuries had a significantly higher GCS than did those with damage to cranial nerve 3. They had less frequent need for inpatient rehabilitation than did those with cranial nerve 6 injury. On the other hand, they had more frequent extremity injuries than did all subgroups.

**DISCUSSION**

This study generally supports the findings gleaned from smaller, uncontrolled studies of ocular motor palsies in CHI.
TABLE 1. Comparison of Cranial Nerve Injury Group to Control Group

<table>
<thead>
<tr>
<th></th>
<th>Closed head Injury with Cranial Nerve Injury (Cranial Nerve Injury Group)</th>
<th>Closed Head Injury without Cranial Nerve Injury (Control Group)</th>
<th>P values ≤ 0.15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>31.4 (19.6), n = 95</td>
<td>27.66 (18.2), n = 71</td>
<td>0.07</td>
</tr>
<tr>
<td>Men</td>
<td>51/95</td>
<td>48/71</td>
<td>0.13</td>
</tr>
<tr>
<td>Loss of consciousness</td>
<td>53/63</td>
<td>46/63</td>
<td></td>
</tr>
<tr>
<td>Glasgow Coma Scale</td>
<td>9.39 (4.7), n = 74</td>
<td>13.00 (3.93), n = 71</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Type of injury</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Collision</td>
<td>9/87</td>
<td>11/71</td>
<td>0.04</td>
</tr>
<tr>
<td>Motor vehicle accident</td>
<td>72/87</td>
<td>54/71</td>
<td>0.02</td>
</tr>
<tr>
<td>Car versus pedestrian</td>
<td>6/87</td>
<td>6/71</td>
<td></td>
</tr>
<tr>
<td>Ocular injury</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Globe</td>
<td>2/95</td>
<td>1/71</td>
<td></td>
</tr>
<tr>
<td>Adnexal</td>
<td>11/95</td>
<td>2/71</td>
<td>0.04</td>
</tr>
<tr>
<td>Optic nerve</td>
<td>7/95</td>
<td>0/71</td>
<td>0.02</td>
</tr>
<tr>
<td>Pupil</td>
<td>3/95</td>
<td>0/71</td>
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<tr>
<td>Systemic injury</td>
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<td>Soft tissue</td>
<td>46/95</td>
<td>40/71</td>
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<td>Chest</td>
<td>32/95</td>
<td>9/71</td>
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<tr>
<td>Abdominal</td>
<td>12/95</td>
<td>12/71</td>
<td></td>
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<tr>
<td>Extremity</td>
<td>32/95</td>
<td>21/71</td>
<td></td>
</tr>
<tr>
<td>Intracranial injury (any)</td>
<td>62/93</td>
<td>5/71</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Frontal</td>
<td>18/93</td>
<td>1/71</td>
<td>0.0002</td>
</tr>
<tr>
<td>Temporal</td>
<td>18/93</td>
<td>1/71</td>
<td>0.0002</td>
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<td>9/93</td>
<td>0/71</td>
<td>0.0055</td>
</tr>
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<td>Tentorial</td>
<td>5/93</td>
<td>1/71</td>
<td>0.04</td>
</tr>
<tr>
<td>Interpeduncular</td>
<td>6/93</td>
<td>0/71</td>
<td></td>
</tr>
<tr>
<td>Occipital</td>
<td>0/93</td>
<td>1/71</td>
<td></td>
</tr>
<tr>
<td>Cervical spine injury</td>
<td>6/93</td>
<td>3/71</td>
<td></td>
</tr>
<tr>
<td>Other spine injury</td>
<td>9/93</td>
<td>4/71</td>
<td></td>
</tr>
<tr>
<td>Craniofacial fracture (any)</td>
<td>46/93</td>
<td>9/71</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Orbital</td>
<td>19/93</td>
<td>4/71</td>
<td>0.007</td>
</tr>
<tr>
<td>Facial</td>
<td>25/93</td>
<td>8/71</td>
<td>0.01</td>
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<tr>
<td>Calvarial</td>
<td>35/93</td>
<td>1/71</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Skull base</td>
<td>33/93</td>
<td>2/71</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Inpatient rehabilitation</td>
<td>59/95</td>
<td>13/71</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Outpatient rehabilitation</td>
<td>14/95</td>
<td>7/71</td>
<td></td>
</tr>
</tbody>
</table>

Numbers in parentheses represent one standard deviation from the mean.
N/A, not applicable.

We found that patients with CHI and ocular motor cranial nerve palsy had sustained more severe head trauma than had patients without ocular motor cranial nerve palsy, as judged by a relatively low initial GCS, higher rates of intracranial and craniofacial imaging abnormalities, and worse short-term neurological outcomes, as judged by the relatively greater frequency of inpatient rehabilitation. Our Cranial Nerve Injury Group tended to have poorer physical therapy scores, which suggests a worse clinical outcome than in the Control Group.

In the comparison between the subgroups of cranial nerve palsy patients, those with cranial nerve 3 palsy had suffered relatively severe head trauma (as measured by GCS), worse clinical outcomes (as measured by bed mobility and gait scores), and higher rates of temporal...
region intracranial imaging abnormalities. Those with cranial nerve 4 palsy had an intermediate level of head trauma, and those with cranial nerve 6 palsy had the lowest severity of head trauma. Surprisingly, those with multiple ocular motor cranial nerve palsies had a relatively low severity of head injury (as measured by GCS) but the highest frequency of extremity injuries.

Although ocular motor cranial nerve palsy was associated with a relatively low GCS and more craniofacial imaging abnormalities, these patients did not have a greater rate of LOC, the rates being over 80% in CHI patients with and without ocular motor cranial nerve palsy. An earlier study (6) had found that LOC is relatively common in CHI patients with various neuro-ophthalmic manifestations including ocular motor nerve injury, but no comparison was made to head-injured patients without neuro-ophthalmic findings. We infer that the GCS and imaging studies are better predictors of the presence of an ocular motor palsy than LOC, which may occur at too mild a level of CHI to be a useful discriminator.

With respect to craniofacial fractures, our study is consonant with three smaller studies (7–9) that demonstrated a greater than 50% frequency of craniofacial fractures in head-injured patients with ocular motor cranial nerve palsies. However, a small series found a less than 50% frequency of orbital fractures (10) and another found a less than 50% frequency of craniofacial fractures of any region (11).

Cranial Nerve 3 Palsy

Our data confirm the suggestion from smaller reports that cranial nerve 3 palsy is associated with relatively severe CHI. A study by Elston (7) demonstrated that among 20 patients with traumatic cranial nerve 3 palsy, all had LOC. Ing (12) characterized all 20 of his patients with traumatic cranial nerve 3 palsy as having serious injury but presented no supportive data. These earlier reports had, unlike our study, dealt only with single cranial nerve injuries without comparison to other cranial nerve injuries or to head-injured patients without cranial nerve injury. Our study also confirms the findings of earlier small studies (7,11,12) that motor vehicle accidents account for most of the head injuries leading to traumatic cranial nerve 3 palsy.

Cranial Nerve 4 Palsy

We found that CHI patients with cranial nerve 4 palsy had an intermediate severity of head injury. Our findings are in line with the study of Younge (13) who reported that 14 of 16 patients had suffered coma or concussion. But our study differs from two studies suggesting that traumatic cranial nerve 4 is often associated with relatively mild CHI. Khawan (14) reported that only two of 27 patients had LOC lasting beyond 30 minutes. Teller (15) reported that only two of 24 patients had LOC and that 11 had suffered minor head trauma based on direct questioning.

Cranial Nerve 6 Palsy

Our finding that cranial nerve 6 palsy patients had the lowest degree of head injury is at variance with the common concept that, among injuries to the three ocular motor cranial nerves, injury to cranial nerve 6 injury is associated with relatively severe CHI. For example, Crouch (16) found that 18 of 20 patients with traumatic cranial 6 nerve palsy had suffered LOC.

Multiple Ocular Motor Nerve Palsies

Our study surprisingly found that patients with bilateral cranial nerve 4 injuries had a relatively minor degree of head injury, differing from the series of Sydnor (17) and Chapman (18) in which nearly all patients had suffered LOC. An earlier head trauma study (19) had found...
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<th>Cranial Nerve Injury Subgroups</th>
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<td><strong>Men</strong></td>
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<td>23/32</td>
<td>12/25</td>
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<td>CN 3 v CN 4, P = 0.01</td>
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<td>Glasgow Coma Scale</td>
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<td>CN 3 v CN 6, P = 0.01</td>
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<td>Type of injury</td>
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<td>CN 3 v Multiple, P = 0.05</td>
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<td>Motor vehicle accident</td>
<td>19/21</td>
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<td>10/32</td>
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<td>Temporal region</td>
<td>9/21</td>
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<td>Inpatient rehabilitation</td>
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<td>Total scores (on admit)</td>
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<td></td>
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<td>CN 6 v CN 4, P = 0.03</td>
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<td>Bed mobility</td>
<td>3.8 (0.4), n = 20</td>
<td>3.2 (1.1), n = 30</td>
<td>3.3 (1.1), n = 24</td>
<td>3.3 (0.9), n = 26</td>
<td>CN 3 v CN 4, P = 0.02</td>
</tr>
<tr>
<td>Gait</td>
<td>4.0 (2.1), n = 20</td>
<td>3.6 (0.9), n = 30</td>
<td>3.5 (0.9), n = 24</td>
<td>3.6 (0.7), n = 26</td>
<td>CN 3 v CN 4, P = 0.02</td>
</tr>
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</table>

*All variables with $P < 0.15$ in the four-way comparisons between each of the cranial nerve injury subgroups were subjected to two-way comparisons. We report only the comparisons with $P \leq 0.05$.

Number in parentheses represents one standard deviation from the mean.

PT, physical therapy.

that a high degree of head injury was associated with multiple rather than single ocular motor cranial nerve injuries, but these conclusions were drawn from a comparison of the single, bilateral, and multiple cranial nerve injury groups to each other without a control group.

A disappointing outcome of our study was the lack of correlation between the location of the imaging abnormalities and the type of cranial nerve injury. The closest correlation was the relatively high prevalence of temporal lobe imaging abnormalities in patients with cranial nerve 3 injuries.

The lack of a correlation between imaging abnormalities and a particular cranial nerve palsy precludes any new insights into the mechanism of traumatic ocular motor nerve injury. There is experimental pathologic evidence of injury at three locations: in the brain stem, at the nerve exit from the brain stem, and at the point where the nerves pierce the dura. Epstein and Baker (20) hypothesized that shock waves from the impact site distort the skull, leading to calvarial and basilar skull fractures and movement of the brain. Shock waves or fractures might cause damage to the ocular motor cranial nerves as they pierce the dura to enter the cavernous sinus. Heinze (21) demonstrated injury to the ocular motor nerves at or near their exit from the brainstem in post-mortem examinations of motor vehicle accident victims. Cranial nerve injury inside the brainstem is suggested by post-mortem examinations of trauma patients by Lindenberg (22), who demonstrated that the midbrain is damaged as it is thrust against the stiff tentorium. Such injuries occurred in frontal blows to the head and falls onto the buttocks, but rarely in falls onto the occiput. However, none of the patients of Lindenberg (22) had clinical or pathologic evidence of damage to a cranial nerve. In another study by Lindenberg (23), a patient with traumatic hyperextension of the neck exhibited histopathologic evidence of injury to the brainstem fascicle of cranial nerve 6. Studies by Adams and Gennarelli (24-26) in humans and primates have confirmed that head injury from rapid
deceleration causes diffuse axonal injury in the brain stem, particularly in the midbrain.

**Proposed Mechanisms of Traumatic Cranial Nerve 3 Injury**

Pathologic reports have demonstrated injury to cranial nerve 3 at its exit from the brainstem (21), from the superior orbital fissure (21), and at the tentorial shelf after herniation secondary to traumatic brain edema (27). Balcer (28) reported a case of traumatic cranial nerve 3 palsy with an MRI finding of hemorrhage at the midbrain exit site of cranial nerve 3. Hooper (10) reported that 11 of 12 patients with cranial nerve 3 injuries had suffered a blow to the central frontal region of the head. Our study failed to disclose midbrain imaging abnormalities, but CT was the standard modality, which is less sensitive than MRI to hemorrhagic contusion. The relatively common rate of temporal region imaging abnormalities in our study (43% of patients) may implicate this region in injury to cranial nerve 3.

**Proposed Mechanisms of Traumatic Cranial Nerve 4 Palsy**

Post-mortem examinations of patients in motor vehicle accidents have demonstrated injury to cranial nerve 4 at its exit from the brainstem in the dorsal midbrain (21). Coppeto (29) reported two patients with traumatic cranial nerve 4 palsy and contralateral Horner syndrome with CT evidence of parenchymal contusion of the dorsolateral midbrain at the ponto-mesencephalic junction. Lavin (30) reported a patient with cranial nerve 4 palsy who had CT evidence of a hematoma near the superior cerebellar cistern. He hypothesized that the hemorrhage was secondary to bleeding from a small vessel dashed against the tentorium, similar to the mechanism proposed by Lindenberg (22). Burgerman (31) reported a patient with traumatic cranial nerve 4 palsy and MRI evidence of a parenchymal contusion in the dorsal midbrain with a previously negative CT. In a study of 13 patients with cranial nerve 4 injury, Burger (32) found that those with unilateral cranial nerve 4 palsy had suffered frontolateral blows, whereas those with bilateral cranial nerve 4 injury had suffered midfrontal blows. We lacked the information about the site of the head blows in our study. We did not find any midbrain hemorrhages.

**Proposed Mechanisms of Traumatic Cranial Nerve 6 Palsy**

There are two hypotheses as to the mechanism of injury in traumatic cranial nerve 6 palsies: petrous bone injury transmitted to the nerve in that region and neck hyperextension causing stretch of the nerve. Lateral crushing injuries to the skull have been shown in the laboratory (33) to cause fracture of the apex of the petrous portion of the temporal bone. A subsequent pathologic study (34) found traumatic injury to cranial nerve 6 as it passes over this region. Clinical reports of bilateral compression injuries in cranial nerve 6-injured patients support this mechanism (10,35).

Lindenberg (23) described a patient with a traumatic neck hyperextension who had pathologic evidence of injury to the pontine segment of the sixth cranial nerve. Schneider (36) reported two cranial nerve 6-injured patients following traumatic neck hyperextension in a motor vehicle accident who had suffered cervical vertebral but no craniofacial fractures. He hypothesized that the injury was secondary to upward and posterior displacement of the brainstem causing stretch injury to the sixth cranial nerve as it passes through Dorello's canal under the rigid petrosphenoidal ligament. Neither of these studies (23,36) provides information as to the location of the blow. In two other reports, the mechanism is less clear. Rosa (37) described a patient with severe frontal trauma and neck hyperextension who suffered cranial nerve 6 injury. In Hooper's series (10) of six patients with traumatic cranial nerve 6 injury, four had a frontolateral blow, one had a midfrontal blow, and one had a lateral compression injury.

We found no difference in the distribution of craniofacial fractures or intracranial injury on CT imaging to suggest a particular location of injury, nor did we find a difference in the rate of cervical spine injury in the cranial nerve-injured group, although this does not rule out traumatic neck hyperextension as a mechanism of injury.

We are mystified at the finding that our patients with multiple or bilateral cranial nerve injuries had a relatively low level of severity of trauma as measured by the GCS. Interestingly, this group sustained the highest frequency of extremity injuries. The mechanism of injury in single and multiple cranial nerve damage may be different.

Our study supports earlier reports that low levels of CHI, as determined by lack of LOC, are unlikely to cause cranial nerve palsy. Walter (38) reported two patients with head trauma and cranial nerve 3 injuries without LOC or associated injuries who were later found to have posterior communicating artery aneurysms. Eyster (39) reported three patients with cranial nerve 3 injuries in a setting of head trauma insufficient to cause LOC who were eventually found to have basal intracranial tumors. In another report (40), neoplasms were found at the base of the brain in a series of three patients with cranial nerve 4 palsy in the setting of minor head trauma. A patient with cranial nerve 4 palsy and minimal head trauma without LOC was found to have a tentorial arteriovenous malformation compressing the subarachnoid portion of the nerve (41). This information suggests that, in the setting of a cranial palsy following minimal head trauma, other etiologies should be sought.
We acknowledge two sources of accrual bias that might have affected our results: 1) all patients were drawn from a tertiary care medical center, which might have excluded patients with milder forms of CHI; and 2) the Cranial Nerve Injury and Control Groups were not drawn from identical sources. The Cranial Nerve Injury Groups included patients drawn from outpatient clinics and the emergency room whereas the Control Group patients were drawn entirely from the emergency room. We also recognize that many statistical comparisons were made between the case and control groups and subsets thereof, and that this practice can lead to falsely positive findings by chance alone. We have tried to avoid this trap by using the Bonferroni adjustment and by adhering to the clinical relevance of statistical findings. Having done so, we believe that our data have sufficient validity to provide useful information to the clinician.

REFERENCES

Resolution of Homonymous Visual Field Loss Documented with Functional Magnetic Resonance and Diffusion Tensor Imaging

Masaki Yoshida, MD, PhD, Masahiro Ida, MD, Thien Huong Nguyen, MD, PhD, Marie-Therese Iba-Zizen, MD, Luc Bellinger, MD, Jean Louis Stevenart, MD, Takehiko Nagao, MD, Shinsuke Kikuchi, MD, Takaaki Hara, MD, Takuya Shiba, MD, Kenji Kitahara, MD, PhD, and Emmanuel Alain Cabanis, MD, PhD

Abstract: A 68-year-old man developed right homonymous hemianopic paracentral scotomas from acute infarction of the left extrastriate area. He was studied over the ensuing 12 months with visual fields, conventional MRI, functional MRI (fMRI), and diffusion tensor imaging (DTI). As the visual field defect became smaller, fMRI demonstrated progressively larger areas of cortical activation. DTI initially showed that the lesioned posterior optic radiations were completely interrupted. This interruption lessened in time and had disappeared by one year after onset. fMRI and DTI are innovative measures to follow functional and structural recovery in the central nervous system. This is the first reported application of these imaging techniques to acute cerebral visual field disorders.

(Cerebral lesions that involve the retrochiasmal visual pathway can cause contralateral visual field defects. As many as 50% of patients with such lesions show at least some spontaneous recovery (1). This recovery is normally assessed with visual field testing.

Functional magnetic resonance imaging (fMRI) is a non-invasive technique that can be used to investigate brain function with good spatial and temporal resolution. fMRI indirectly monitors modulated local blood oxygenation levels associated with neural activity (2). The effectiveness of fMRI for assessing visual dysfunction, especially that caused by stroke, has not been confirmed.

Diffusion tensor imaging (DTI) is a recently developed technique in which diffusion anisotropy is quantitatively measured as the incoherent directional distribution of free water diffusibility on each voxel as a diffusion ellipsoid (3). Because this ellipsoid closely resembles axonal fibers, a fiber tract map can be created to display the axonal network when the shape and orientation of ellipsoids are similar between neighboring voxels (4).

We report a patient with right homonymous hemianopic paracentral scotomas in whom MRI showed an acute infarct involving the left occipital lobe. As the visual field defects gradually improved, fMRI showed improved ipsilateral cortical activation and DTI showed reconstitution of the lesioned optic radiations.

CASE REPORT AND STUDY METHODS

Clinical Features

A 68-year-old man with atrial fibrillation who had been treated with anticoagulation therapy reported the sudden onset of cloudiness of the right visual field. Forty-eight hours later, ophthalmologic examination disclosed a best-corrected visual acuity of 20/25 OD and 20/20 OS. Right homonymous hemianopic paracentral scotomas were observed with Goldmann kinetic perimetry (Fig. 1). The patient then underwent the following serial imaging studies:

Conventional MRI

MRI was performed with a 1.5-T clinical scanner (Magnetom Vision, Siemens, Erlangen, Germany) with the use of a head coil. Three-dimensional time-of-flight magnetic resonance (MR) angiography (3-D TOF-MRA) was also performed. After these conventional MR data were acquired, fMRI, DTI, and 3-D inversion-recovery T1-weighted anatomical imaging (magnetization prepared rapid acquisition gradient-echo [MPRAGE]) were performed. The MPRAGE images were obtained with the following...
FIG. 1. Goldmann perimetry performed two days after stroke shows right homonymous hemianopic scotomas.

parameters: 10.3 milliseconds/300 milliseconds/300 milliseconds/1 (repetition time [TR]/echo time [TE]/spin lattice relaxation time [TI]/excitations); flip angle 15°; matrix 256 × 256; field of view 210 × 210 mm; slice thickness 2.5 mm; and number of sections 80.

**Functional MRI**

fMRI was performed with a single-shot, gradient-echo, echo-planar sequence with the following parameters: echo time 60 milliseconds, repetition time 3000 milliseconds, flip angle 90°; matrix 64 × 64; field of view 210–240 mm, slice thickness 4 mm. Twenty-five axial images, including images of the entire brain parallel to the calcarine fissure, were obtained.

For fMRI, all stimuli were generated on a personal computer using homemade software. A liquid crystal display projector (TLP411J, Toshiba Corp., Tokyo, Japan) with a resolution of 800 × 600 pixels was used to project these stimuli onto a front-projection screen. The patient viewed the stimuli via an adjustable mirror angled at 45° to the line of sight.

For the stimulation condition, a black-and-white checkerboard reversing at 8 Hz was used. Each square of the checkerboard subtended a visual angle of 0.75° in height and width. The mean luminance of the checkerboard projection was 75 candela/m² and its contrast was close to 90%.

Three types of stimuli were presented. In the resting phase, a central fixation point was projected on a gray background with the same mean luminance as the checkerboard. In succession, a horizontal wedge-shaped checkerboard with 30° of polar angle was projected on the right visual field, and a round, centrally-positioned checkerboard subtending 15° of visual angle was projected onto the central fixation point.

Each experimental run consisted of the acquisition of 120 volumes, with volume acquisition for three seconds, giving a total run time of six minutes. The 120 volumes were divided into 15 blocks of eight volumes, corresponding to five iterations of three phases; a rest phase was followed by an Activation 1 phase and an Activation 2 phase. Each phase contained eight volumes for a duration of 24 seconds. In the first block—the rest phase—the fixation point was projected. In the second and third blocks—the Activation 1 and 2 phases—the wedge-shaped checkerboard on the right visual field and round checkerboard were presented. In this binocular vision investigation, the subject's task was to fix on the central dot during the rest and activation phases.

**Diffusion Tensor Imaging**

DTI was performed with a single-shot, spin-echo, echo-planar sequence with the following parameters: echo time 100 milliseconds, repetition time 4000 milliseconds; matrix 128 × 128 interpolated 256 × 256; field of view 220 × 220 mm; slice thickness 20 interleaved contiguous 5 mm; diffusion gradient 6 directions with the b 1000 s/mm² as the peak and also b 0 s/mm for T2-weighted images. The total run time of DTI was 96 seconds with three excitations.

**Data Analysis**

The fMRI data were analyzed with a conventional personal computer (Windows 2000 operating system, Pentium IV 1.5-GHz processor, 768 megabytes random access memory), our own Image Calculator V0.44 software, and the SPM2 software package (Wellcome Department of Imaging Neuroscience, University College London, London, UK) (5). The images were transformed with Image Calculator V0.44 software into analyze format for further treatment with SPM2 software.

Functional images of each experiment were realigned and transformed into the anatomical space defined by Talairach and Tournoux (6). These two steps were
performed under standard parameters (default settings) suggested for the SPM2 software. The images were spatially smoothed with a Gaussian filter (full width at half maximum = 6 mm in three directions). A box-car design with the hemodynamic response function (hrf) was used. Two comparisons were made for each experiment: Contrast I, in which the first block (fixation point only, R) was compared with the second block (wedge-shaped right visual field stimulation, Activation 1) to evaluate residual left cortical function, and Contrast II, in which the first block (fixation point only, R) was compared with the third block (a centrally-positioned circle subtending 15° of visual angle, Activation 2) to compare affected left cortical function with unaffected right cortical function. For statistical comparison, differences with corrected $P$ values < 0.05 with multiple testing at the voxel level and the 50-voxel extended threshold were considered significant.

The DTI data were analyzed with the same personal computer, VOLUME-ONE VI.56 software program, the diffusion TENSOR visualizer (dTV) VI.5 software program (7). These software programs were developed by the Image Computing and Analysis Laboratory, Department of Radiology, University of Tokyo (http://www.ut-radiology.umin.jp/). The distortion of raw data images (7) was not corrected before DTI data were analyzed. Practical analysis of these software programs is demonstrated by example in a healthy subject (Fig. 2). To visualize the optic radiations, we drew a region of interest as a seed on green areas, which corresponded to the major eigenvector perpendicular to this plane resulting from dTV software (Fig. 2A) on a coronal section between the trigone and the posterior horn of the lateral ventricle (Fig. 2B). To trace axonal projections, the tensor was tracked and lines were drawn in both antegrade and retrograde directions in 3-D space from seeds along the major eigenvector. The optic radiations were shown to reach both occipital poles (Fig. 2C).

**RESULTS**

**Visual Fields**

Goldmann kinetic perimetry performed one month after onset disclosed marked improvement of the right homonymous visual field deficit (Fig. 3).

**Conventional MRI**

On initial imaging two days after onset, the lesion in the left occipital lobe appeared as a high-intensity area in an extrastriate cortical area on diffusion-weighted imaging (DWI) (Fig. 4A), FLAIR (Fig. 5A), and T2-weighted images. On the ninth day after onset, repeat MRI showed lower signal intensity on DWI (Fig. 4B) and a smaller area of high-intensity signal on FLAIR (Fig. 5B).

**FIG. 2.** Diffusion tensor imaging (DTI) fiber tracking of optic radiations in a healthy subject. We drew a region of interest as a seed on green areas (white arrow) which correspond to the major eigenvector direction perpendicular to this plane (A) and on a coronal section between the trigone and the posterior horn of the lateral ventricle (B). The tensor was tracked, and lines were drawn in both antegrade and retrograde direction in three-dimensional space; the optic radiations are shown to reach both occipital poles (C).
Functional MRI

fMRI data were acquired two days after onset, nine days after onset, 30 days after onset, and one year after onset (Fig. 6). The Contrast I experiment (Fig. 6, top) demonstrated progressively larger areas of left cortical activation (two days after onset, 384 voxels; nine days after onset, 449 voxels; 30 days after onset, 716 voxels; one year after onset, 1540 voxels). The center of activation was displaced from the first acquisition (two days after onset; x/y/z: -12/-90/-4) to a more posterior portion of the Talairach space (6) on the second acquisition (−14/-98 or −100/4), which was consistent with the left occipital pole. The Contrast II experiment (Fig. 6, bottom), designed to simultaneously evaluate the visual cortices of both the affected and unaffected cerebral hemispheres, showed broadest activation two days after onset (two days after onset, 5,979 voxels; nine days after onset, 1,957 voxels; four weeks after onset, 4,109 voxels; one year after onset, 4,580 voxels). The activated visual areas of the unaffected right hemisphere were most diffuse two days after onset, were smallest nine days after onset, and demonstrated consistent increases across sessions. The ratios of the sizes of activated visual areas on the left and right sides demonstrated decreasing asymmetry (two days after onset, L:R ratio = 0.12, 640-5,339 voxels; nine days after onset, L:R ratio = 0.26, 403-1,554 voxels; four weeks after onset, L:R ratio = 0.37, 1109-3,000 voxels; one year after onset, L:R ratio = 0.79, 2,021-2,559).

Diffusion Tensor Imaging

DTI data were analyzed to track the optic radiations two days after onset, nine days after onset, and one year after onset, 30 days after onset, and one year after onset (Fig. 6). The Contrast I experiment (Fig. 6, top) demonstrated progressively larger areas of left cortical activation (two days after onset, 384 voxels; nine days after onset, 449 voxels; 30 days after onset, 716 voxels; one year after onset, 1540 voxels). The center of activation was displaced from the first acquisition (two days after onset; x/y/z: -12/-90/-4) to a more posterior portion of the Talairach space (6) on the second acquisition (−14/-98 or −100/4), which was consistent with the left occipital pole. The Contrast II experiment (Fig. 6, bottom), designed to simultaneously evaluate the visual cortices of both the affected and unaffected cerebral hemispheres, showed broadest activation two days after onset (two days after onset, 5,979 voxels; nine days after onset, 1,957 voxels; four weeks after onset, 4,109 voxels; one year after onset, 4,580 voxels). The activated visual areas of the unaffected right hemisphere were most diffuse two days after onset, were smallest nine days after onset, and demonstrated consistent increases across sessions. The ratios of the sizes of activated visual areas on the left and right sides demonstrated decreasing asymmetry (two days after onset, L:R ratio = 0.12, 640-5,339 voxels; nine days after onset, L:R ratio = 0.26, 403-1,554 voxels; four weeks after onset, L:R ratio = 0.37, 1109-3,000 voxels; one year after onset, L:R ratio = 0.79, 2,021-2,559).

FIG. 4. Axial diffusion-weighted imaging (DWI). A. Performed two days after onset, DWI shows a high-intensity area (white arrow) corresponding to the left occipital lobe infarct. B. Performed nine days after onset, DWI shows decreased signal intensity and smaller areas of hyperintensity as compared to A.
DISCUSSION

Although several papers have described fMRI and DTI findings in patients with cerebral visual field disorders (8,9), we are not aware of any reports of longitudinal fMRI or DTI studies of acute cerebral infarction producing homonymous hemianopia.

In our patient, fMRI results showed progressive increase in the activated areas of the affected left hemisphere consistent with functional recovery and progressive decrease in the activated areas in the unaffected right hemisphere associated with recovery. Metabolic change after acute stroke can result in widespread areas of cortical hyperexcitability in regions structurally connected to the lesion in both hemispheres as a consequence of down-regulation of the gamma amino butyric acid (GABA) receptor subunit and a decrease in GABAergic inhibition (10), resulting in increased diffuse blood oxygenation level-dependent signals. When comparing task-related brain activation in the acute and chronic phases of motor recovery after stroke, positron emission tomography (11,12) and fMRI (13,14) data demonstrate greater and more widespread brain activation in early stages than in later stages. This widespread cortical activation, including the bilateral primary motor cortices (M1), decreases with recovery (13). Patients with poorer recovery tend to recruit more cortical regions during motor performance, and motor recovery is negatively correlated with task-related cortical activation (15).

In the Contrast II experiment, the activated visual areas of the healthy right hemisphere were most diffuse 48 hours after onset. This finding suggests that the affected left hemisphere recruits more cortical regions to the healthy right hemisphere during the acute phase.

In our patient, the DTI fiber tract map of the left optic radiation was interrupted at the area of infarction corresponding to an area of high signal intensity that appeared like a white cloud caused by cellular and/or stromal edema within the acute infarction. Acute cerebral infarction causes reduced diffusion anisotropy (16), which can produce a fiber-tracking defect. Consistent with disappearing areas of high signal intensity, fiber tract maps one year after onset showed an intact optic radiation in the infarcted left hemisphere.

Although several studies have evaluated axonal function after stroke using fiber tract mapping (17,18), this technique requires further refinement before it can be used to quantitatively evaluate axonal dysfunction and its consequences. Nevertheless, fiber tract maps showed that the infarcted area in our patient was located on the main trajectory of the left optic radiation, which was morphologically reconstituted one year after onset.

Our results suggest that fMRI and DTI are useful for investigating cerebral visual field disorders, including those in the acute phase.
FIG. 6. Longitudinal functional MRI (fMRI) results. Top: Contrast I experiment demonstrates progressively larger areas of activation corresponding to the left striate cortex. On the second acquisition, the center of activation is displaced to a more posterior portion of the Talairach space as compared to the first acquisition. Bottom: Contrast II experiment shows broadest activation two days after onset. The activated visual areas of the unaffected right hemisphere are most diffuse two days after onset, smallest nine days after onset, and demonstrate consistent increases thereafter. The ratios of the sizes of activated visual areas of the two cerebral hemispheres demonstrates decreasing asymmetry.
FIG. 7. Diffusion Tensor Imaging (DTI) performed two days after onset (A), nine days after onset (B), and one year after onset (C). A. The optic radiation reaches the occipital pole in the right hemisphere (black arrow) but is completely interrupted in the left hemisphere, corresponding to a high-intensity area that appears like a white cloud caused by local edema (white arrow). B. The left optic radiations are interrupted to a lesser extent at the left cortical lesion (white arrow). C. There is no longer any interruption in the left optic radiations.

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REFERENCES
Relationship between Cognitive Impairment and Retinal Morphological and Visual Functional Abnormalities in Alzheimer Disease

Pervin K. Iseri, MD, Özgül Altına§, MD, Tomris Tokay, MD, and Nurşen Yılıkse, MD

Background: There is conflicting evidence as to whether Alzheimer disease (AD) is accompanied by loss of retinal ganglion cells. To evaluate this issue, we have used optical coherence tomography (OCT) to assess the thickness and volume of the retina. We have also sought to correlate our findings with visual function and cognitive impairment.

Methods: We evaluated 28 eyes of 14 patients with AD and 30 eyes of 15 age-matched control subjects. In these two groups, we measured retinal nerve fiber layer (RNFL) thickness, macular thickness, and macular volume with OCT, visual function through latency of the pattern visual evoked potential (VEP) signal, and cognitive impairment through the Mini-Mental State Examination (MMSE).

Results: The parapapillary and macular RNFL thickness in all quadrants and positions of AD patients were thinner than in control subjects. The mean total macular volume of AD patients was significantly reduced as compared with control subjects (P < 0.05). Total macular volume and MMSE scores were significantly correlated. No significant difference was found in the latency of the VEP P100 of AD patients and control subjects.

Conclusions: Our study confirms some other studies in showing that in AD patients there is a reduction of parapapillary and macular RNFL thickness and macular volume as measured by OCT. The reduction in macular volume was related to the severity of cognitive impairment.

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Alzheimer disease (AD) is the most common degenerative dementia and causes a progressive decline in cognitive function. In most cases, an episodic memory deficit is the predominant initial complaint. As time passes, changes in daily living activities, cognitive functions, and visual disturbances supervene.

Visual disturbances consist of impairment in spatial contrast sensitivity (1), motion perception (2,3), color discrimination (4), and blurred vision (5). Several recent articles have attributed the visual dysfunction in AD to damage in primary visual cortex and to degeneration of higher cortical areas (6–8). Other studies have shown evidence of pre-cortical involvement on the basis of reduction in the number of retinal ganglion cells and axons of the optic nerve (9,10). In contrast to these reports, some histopathologic studies have shown no retinal nerve damage in AD (11,12). Although recent studies have used sophisticated imaging techniques, such as optical coherence tomography (OCT), scanning laser polarimetry, and pattern electroretinography (PERG), to assess the morphologic and functional changes of the retina in AD, disagreement about retinal involvement persists (13–15).

The macula is defined anatomically as that region of the retina where the ganglion cell layer has a thickness of more than one cell. The ganglion cells and retinal nerve fiber layer (RNFL) contribute 30% to 35% of retinal thickness in the macula, where the ganglion cells are known to be most concentrated (16). Blanks et al (17) histologically observed a total decrease of 25% of neurons in the ganglion cell layer at the level of the fovea/parafovea retina in AD. The greatest decrease was in the foveal region. To our knowledge, no previous studies have investigated macular thickness and volume in living AD patients.

OCT is a relatively new non-invasive, non-contact, transpupillary imaging technology that provides high-resolution cross-sectional images of the retina. OCT has been reported to be useful in assessing glaucoma, diabetic neuropathy, and macular edema (18–22).

The aim of this study was to investigate whether a correlation exists between structural (RNFL thickness, macular thickness and volume) and functional (visual evoked potential [VEP]) measures and cognitive impairment in AD.
METHODS

Patient Accrual

We compared 28 eyes of 14 patients with AD to 30 eyes from 15 age-matched control subjects. The AD patients were obtained from the Kocaeli University Neurology Department Dementia Clinic; the control subjects were obtained from the Kocaeli University Eye Diseases Department General Clinic, Kocaeli, Turkey. The patients met criteria for probable AD set by the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (23) and DSM-IV. AD patients had mild and moderate cognitive impairment according to the Clinical Dementia Rating (CDR) scale (24). All participants were free of ocular disease and systemic disorders affecting vision. Informed consent of AD patients was obtained from their first-degree relatives. The research followed the tenets of the Declaration of Helsinki, and the protocol was approved by the local ethics committee.

Neurological Assessments

Each AD patient underwent a detailed neurological examination including laboratory, neuro-imaging evaluations, and psychometric testing. The control subjects also underwent a detailed neurological examination to rule out the presence of cognitive impairment. We excluded patients with dysmetabolic diseases, a history of alcohol abuse, psychiatric disorders, or other neurological diseases. Mini-Mental State Examination (MMSE) (25), Blessed short orientation, and Clock drawing tests for clinical evaluation were used to assess cognition in AD and control subjects.

Ophthalmological Assessments

All AD patients and control subjects underwent a complete ophthalmologic examination, including assessment of visual acuity, refraction, ocular motility, pupillary reflexes, anterior and posterior segment biomicroscopy, applanation tonometry, dilated fundus examination, and Octopus 101 perimeter program G2 visual field testing. The visual field results were uniformly normal in AD and control subjects. All participants had a corrected visual acuity of 5/10 or better with a refractive error between ±3 sph. diopters and intraocular pressures less than 22 mmHg. Eyes with posterior pole pathology such as macular degeneration, glaucoma suspect, or glaucoma, or patients with media opacification such as cataract that prevented ocular and OCT examination were excluded.

Visual Evoked Potential Examination

All AD patients and control subjects underwent VEP examination. The VEP was generated using a black-and-white checkerboard pattern on a television monitor with a dimension of 5 x 5 cm for every check under the following conditions: contrast 95%, check size subtense 50°, reversal rate 2 sec⁻¹, mean luminance 12 Cd.m⁻², field size 17° x 14°. One hundred stimulus epochs of 200 ms were obtained in each average and the amplifier bandwidth was 1-100 Hz.

Patients sat one meter away from the monitor. Ag/AgCl cup-shaped electrodes fixed with collodion were placed over the left and right occiputs at O1 and O2 with a common reference at Fpz and a ground on the left arm. The patients' gaze was fixed on a point at the center of the television monitor monocularly. The bioelectric signal was filtered (bandpass 0.5-200 Hz). Two hundred responses were averaged for every trial (Neuropack Nihon Kohden, MEB-5504 K, Tokyo, Japan). The analysis time was 250 milliseconds. Sweep length was 300 milliseconds (30 msec/div) and stimulus rate was 1 Hz. The normal range of P100 peak latency is 100.26 ± 7.04 milliseconds based on testing of normal controls in our laboratory. Peak latencies of the P100 component were measured.

Optical Coherence Tomography Examination

All AD patients and control subjects underwent OCT examination. The RNFL thickness, and macular thickness and volume were measured by OCT Model 3000 unit (Model 3000, software version A1.1, Carl Zeiss Meditec, Inc., Dublin, California, USA) after pupillary dilatation. Tomography images were constructed from a series of axial reflectance profiles (A-scans) over 2 mm of depth in less than 1 second. Retinal thickness and RNFL thickness were calculated by processing the cross-sectional images using computer algorithms to detect boundaries by searching each A-scan for the highest rates of changes in reflectivity. The software allows the mapping of the thickness data according to quadrant-by-quadrant and clock-hour analyses. Retinal thickness was determined by computer as the distance between the first reflection at the vitreo-retinal interface and the anterior boundary of the second reflective layer, corresponding to the retinal pigment epithelium and the choriocapillaris. RNFL thickness was automatically assessed by computer assuming the correlation with the red highly reflective layer at the vitreo-retinal interface. The posterior margin of the RNFL was automatically located by starting within the photoreceptor layer (posterior) and searching forward in the image (19,26,27).

Throughout scanning, the patient kept both eyes constantly fixed on an internal target provided by the equipment. Each subject eye underwent fast RNFL and macula scan protocols. Mean OCT values were calculated from the values of the three scans. One of the authors (OA) performed the image acquisition and judged its quality. Scans with poor image quality were defined as scans with signal-to-noise...
ratio of less than 45dB or excessive eye movement during measurement. We excluded three patients who had difficulty in cooperating with testing.

The fast RNFL scan protocol consisted of three consecutive 360° circular scans with a diameter of 3.4 mm centered on the optic disc, each containing 256 A-scans taken in a single session of 1.92 seconds. The parapapillary RNFL thickness parameters evaluated in this study were average thickness (360° measurement), temporal quadrant thickness (316° to 45°), superior quadrant thickness (46° to 135°), nasal quadrant thickness (136° to 225°), inferior quadrant thickness (226° to 315°), and thickness for each 12:00 position with the 3:00 as nasal, 6:00 position as inferior, 9:00 as temporal, and 12:00 position as superior.

The fast macula scan protocol consisted of six consecutive 6 mm radial line scans centered on the macula, each containing 128 A-scans taken in a single session of 1.92 seconds. Six sets of intersecting and equally spaced scans were obtained, each crossing the central fovea. The retinal thickness/volume tubular analysis program was used to evaluate macular scans. This analysis program presents mean foveal thickness and total macular volume in 3.5 and 6.00 mm macular maps. Macular retinal thickness data were displayed in three concentric circles. The central disk was the foveal region measuring 1.00 mm in diameter. The inner and outer rings were each divided into four quadrants; the rings had diameters of 3 mm and 6 mm, respectively, in 6.00 mm macular maps. An average retinal thickness and volume were reported for each of the nine regions.

Statistical Analysis
The data are reported as mean values ± standard deviation (SD). The differences between AD and control eyes were statistically evaluated with the Student t test. To assess whether a correlation existed between OCT, VEP, and clinical severity of disease, Pearson's correlation test was used. P < 0.05 was considered significant.

### RESULTS
The mean ages of AD and control groups were 70.1 ± 9.7 years and 65.1 ± 9.8 years, respectively. There was no statistically significant difference in age and gender between groups. Demographic and clinical data of AD and control groups are shown in Table 1. Examples of OCT and VEP recordings from control and AD eyes are shown in Figure 1.

<table>
<thead>
<tr>
<th>TABLE 1. Demographic and clinical data of groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td>MMSE (mean ± SD)</td>
</tr>
<tr>
<td>VEP P100 (mean ± SD)</td>
</tr>
<tr>
<td>Amplitude</td>
</tr>
</tbody>
</table>

*P < 0.01.

AD, Alzheimer disease; MMSE, Mini-Mental State Examination; SD, standard deviation; VEP, visual evoked potential.

compared with control subjects (113.16 ± 6.72 μm) (P < 0.05) (Table 2). The RNFL thickness in all quadrants and positions of AD patients was thinner than in control subjects. RNFL differences were statistically significant (P < 0.05) except in the temporal quadrant, 8:00 and 9:00 positions (Table 1).

The retinal thickness in all quadrants of the macula of AD patients was less than in control subjects. This thinning was prominent in the nasal, temporal, and inferior quadrants (P < 0.05) (Table 2). The macular volume of the AD patients was less than that of control subjects in all macular regions except the foveal minimum. The reduction in macular volume was statistically significant except in the nasal and inferior inner quadrants and the temporal and superior outer quadrants of the macula. The mean total macular volume of AD patients (6.80 ± 0.41 mm³) was significantly reduced when compared with that of control subjects (7.10 ± 0.23 mm³) (P < 0.05) (Table 1).

Visual Evoked Potentials
No significant difference was found in the latencies and amplitudes of the VEP P100 of AD patients (107.96 ± 9.93 msec) (16.35 ± 2.69 μV) and control subjects (107.80 ± 10.40 msec) (18 ± 3.59 μV) (P > 0.05) (Table 1).

Correlation between Optical Coherence Tomography, Visual Evoked Potential, and Mini-Mental State Examination
A highly significant correlation was found between total macular volume and MMSE scores in AD patients (r = 0.696; P = 0.006) (Fig. 2). There was no correlation between OCT and VEP changes (Table 3).
Alzheimer Disease


FIG. 1. Example of retinal nerve fiber layer (RNFL) thickness in one eye of a patient with Alzheimer disease (AD) (A) and one eye of a control subject (B). Top: Circular optical coherence tomography (OCT) taken in cylindrical section of tissue surrounding the optic disc shows a marked decrease of the RNFL reflection in the eye of the AD patient (A) as compared with the eye of a control subject (B). Bottom: The RNFL thickness in each clock position and the macular thickness in each region are reduced in the AD eye (A) as compared with the control subject eye (B).

DISCUSSION

The results of our study suggest a significant reduction in parapapillary RNFL, macular thickness and volume in patients with AD. We have also demonstrated a highly significant correlation between total macular volume and MMSE scores. Structural changes were not significantly correlated to the VEP changes.

Our data are consistent with histologic studies (9,10) and other methods of evaluating the RNFL and optic nerve in vivo (15,28), which demonstrate substantial decline in the quantity of optic nerve fibers and a degeneration of retinal ganglion cells in AD. Optic disc pallor, pathologic disc cupping, and thinning of the neuroretinal rim and the RNFL have been reported in two clinical studies based on the subjective evaluation of fundus photographs (28,29). Tsai et al (28) have observed an increased cup-to-disc ratio, cup volume, and decreased disc rim area in AD patients by optic nerve analyzer. Parisi et al (15) demonstrated a reduction in RNFL thickness by using OCT and suggested that this morphologic abnormality is related to retinal dysfunction as revealed by abnormal PERG responses.

Our data indicate not only a significant decline in parapapillary RNFL but also in macular thickness and volume in AD eyes. These findings suggest a loss of retinal ganglion cells in AD patients. To our knowledge, no report has previously documented the macular volume and thickness in vivo in AD patients. These findings are in agreement with the postmortem study of Blanks et al (17) demonstrating a total decrease of 25% of neurons in the ganglion cell layer at the level of the foveal and parfoveal retina.

In the pathophysiology of AD, beta-amyloid peptides that are cleaved from the amyloid precursor protein (APP) play a critical role. In the later stages of the disease,

FIG. 2. Correlation plot of the total macular volume and Mini-Mental State Exam (MMSE) scores in our Alzheimer disease (AD) patients shows a high correlation ($r = 0.696$).
beta-amyloid peptides compose the characteristic pathologic findings of AD, including neurofibrillary tangles and neuritic plaques. The cortical degeneration characteristic of AD is present especially in visual association areas. Histopathologic studies have disclosed the pathologic hallmarks of AD (B-amyloid, tau, and APP neurofibrillary tangles and neuritic plaques) in subcortical visual centers, including the lateral geniculate nucleus and superior colliculus (31) but not in the retina (9,30). On the other hand, degeneration of retinal ganglion cells and their axons in the nerve fiber layer has been reported (10). Morphometric analysis has shown that in AD, the optic nerve has

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Location</th>
<th>Alzheimer group (n = 28), mean ± SD</th>
<th>Control group (n = 30), mean ± SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parapapillary RNFL thickness (microns)</td>
<td>RNFL (average)</td>
<td>87.46 ± 23.78</td>
<td>113.16 ± 6.72</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Superior RNFL</td>
<td>112.64 ± 35.32</td>
<td>137.16 ± 16.48</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Inferior RNFL</td>
<td>103.10 ± 33.64</td>
<td>141.56 ± 19.09</td>
<td>0.000</td>
</tr>
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<td></td>
<td>Temporal RNFL</td>
<td>64.92 ± 17.70</td>
<td>72.30 ± 16.42</td>
<td>0.106</td>
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<tr>
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<td>Nasal RNFL</td>
<td>63.57 ± 19.09</td>
<td>96.00 ± 34.39</td>
<td>0.000</td>
</tr>
<tr>
<td>1:00</td>
<td>103.53 ± 40.12</td>
<td>131.43 ± 24.22</td>
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<tr>
<td>2:00</td>
<td>81.00 ± 27.87</td>
<td>114.13 ± 39.26</td>
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<tr>
<td>3:00</td>
<td>49.96 ± 12.78</td>
<td>79.83 ± 39.20</td>
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</tr>
<tr>
<td>4:00</td>
<td>60.39 ± 22.59</td>
<td>95.33 ± 28.69</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>5:00</td>
<td>87.17 ± 26.65</td>
<td>129.83 ± 31.85</td>
<td>0.000</td>
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</tr>
<tr>
<td>6:00</td>
<td>111.96 ± 38.01</td>
<td>153.83 ± 24.71</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>7:00</td>
<td>111.17 ± 44.86</td>
<td>142.06 ± 26.35</td>
<td>0.002</td>
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<tr>
<td>8:00</td>
<td>67.82 ± 21.69</td>
<td>74.03 ± 19.11</td>
<td>0.251</td>
<td></td>
</tr>
<tr>
<td>9:00</td>
<td>51.03 ± 13.11</td>
<td>53.83 ± 12.33</td>
<td>0.406</td>
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<tr>
<td>10:00</td>
<td>76.89 ± 23.95</td>
<td>90.16 ± 22.37</td>
<td>0.033</td>
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<tr>
<td>Thickness at 11:00</td>
<td>117.14 ± 36.60</td>
<td>138.80 ± 27.23</td>
<td>0.013</td>
<td></td>
</tr>
<tr>
<td>12:00</td>
<td>118.35 ± 40.53</td>
<td>142.03 ± 27.17</td>
<td>0.013</td>
<td></td>
</tr>
<tr>
<td>Average foveal/macular thickness (microns)</td>
<td>Fovea</td>
<td>200.46 ± 20.74</td>
<td>218.25 ± 24.68</td>
<td>0.004</td>
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<td>Temporal inner macula</td>
<td>257.57 ± 21.14</td>
<td>267.96 ± 19.35</td>
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<td>Superior inner macula</td>
<td>269.60 ± 23.23</td>
<td>279.13 ± 12.03</td>
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<tr>
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<td>Nasal inner macula</td>
<td>265.46 ± 26.61</td>
<td>277.23 ± 14.51</td>
<td>0.045</td>
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<tr>
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<td>Inferior inner macula</td>
<td>264.78 ± 34.54</td>
<td>280.16 ± 11.78</td>
<td>0.032</td>
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<tr>
<td></td>
<td>Temporal outer macula</td>
<td>224.57 ± 17.60</td>
<td>233.43 ± 14.17</td>
<td>0.039</td>
</tr>
<tr>
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<td>Superior outer macula</td>
<td>245.50 ± 13.01</td>
<td>247.70 ± 9.33</td>
<td>0.460</td>
</tr>
<tr>
<td></td>
<td>Nasal outer macula</td>
<td>245.25 ± 21.82</td>
<td>264.93 ± 12.24</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Inferior outer macula</td>
<td>227.78 ± 23.07</td>
<td>241.36 ± 10.30</td>
<td>0.007</td>
</tr>
<tr>
<td>Foveal/macular volume (cubic mm)</td>
<td>Fovea</td>
<td>0.153 ± 0.01</td>
<td>0.160 ± 0.01</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>Temporal inner macula</td>
<td>0.400 ± 0.03</td>
<td>0.420 ± 0.01</td>
<td>0.006</td>
</tr>
<tr>
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<td>Superior inner macula</td>
<td>0.418 ± 0.03</td>
<td>0.432 ± 0.01</td>
<td>0.081</td>
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<tr>
<td></td>
<td>Nasal inner macula</td>
<td>0.413 ± 0.04</td>
<td>0.430 ± 0.02</td>
<td>0.068</td>
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<tr>
<td></td>
<td>Inferior inner macula</td>
<td>0.410 ± 0.05</td>
<td>0.435 ± 0.01</td>
<td>0.027</td>
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<tr>
<td></td>
<td>Temporal outer macula</td>
<td>1.197 ± 0.11</td>
<td>1.224 ± 0.06</td>
<td>0.272</td>
</tr>
<tr>
<td></td>
<td>Superior outer macula</td>
<td>1.297 ± 0.06</td>
<td>1.315 ± 0.04</td>
<td>0.264</td>
</tr>
<tr>
<td></td>
<td>Nasal outer macula</td>
<td>1.296 ± 0.11</td>
<td>1.394 ± 0.07</td>
<td>0.000</td>
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<tr>
<td></td>
<td>Inferior outer macula</td>
<td>1.183 ± 0.10</td>
<td>1.267 ± 0.06</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Foveal minimum</td>
<td>6.809 ± 0.41</td>
<td>7.106 ± 0.23</td>
<td>0.002</td>
</tr>
</tbody>
</table>

RNFL, retinal nerve fiber layer; SD, standard deviation.
The loss of retinal ganglion cells may be a primary process or a consequence of retrograde neurodegeneration occurring in the cortical regions.

We found no abnormalities in VEP in our AD patients. Normal pattern VEP responses have been described before in AD, although there is evidence that the P2 component of pattern VEP is delayed (32, 33). In an earlier report, progressive increase in the latency of the flash VEP was related to the severity of dementia (33). These findings stem largely from the fact that flash VEP reflects the abnormality of visual association regions of the brain while pattern VEP shows the function of primary visual cortex and visual pathways (34). Sparing of the primary visual cortex with extensive cortical disease has been shown in AD (33) with positron emission tomography and histopathologic studies (35, 36). The normal VEP responses in our study suggest that primary cortical region and optic nerve function is normal despite considerable RNFL loss.

The significant correlation we found between MMSE scores and macular volume as measured by OCT may be useful in providing a basis for further studies evaluating the effect of disease severity on RNFL.

The predominant loss of the largest class of retinal ganglion cells (M-cells) (10).

Table 3: Correlations between visual evoked potential P100 latency, Mini-Mental State Examination score, and optic coherence tomography retinal thickness measures and optic coherence tomography parameters in Alzheimer disease

<table>
<thead>
<tr>
<th>Versus</th>
<th>RNFL average thickness</th>
<th>Foveal thickness</th>
<th>Total macular volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEP P100 latency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correlation coefficient (r)</td>
<td>0.318</td>
<td>-0.096</td>
<td>0.189</td>
</tr>
<tr>
<td>p</td>
<td>0.059</td>
<td>0.627</td>
<td>0.335</td>
</tr>
<tr>
<td>Mini-Mental State Examination score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correlation coefficient (r)</td>
<td>0.071</td>
<td>0.004</td>
<td>0.696</td>
</tr>
<tr>
<td>p</td>
<td>0.510</td>
<td>0.989</td>
<td>0.006</td>
</tr>
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</table>

RNFL, retinal nerve fiber layer; VEP, visual evoked potential.

REFERENCES


Topical Apraclonidine Testing Discloses Pupillary Sympathetic Denervation in Diabetic Patients

Feray Koc, MD, Tulay Kansu, MD, Sevim Kavuncu, MD, and Esin Firat, MD

Background: Autonomic denervation is common in diabetes mellitus (DM). Pupillary sympathetic denervation (PSD) has been found in Horner syndrome following instillation of apraclonidine 0.5%. We have applied this technique to investigate the prevalence of PSD in DM.

Methods: Apraclonidine 0.5% was instilled in the eyes of 50 patients with DM and 30 age-matched and gender-matched subjects without DM (control subjects). Pupil diameters (PD) were measured before and 60 minutes after instillation. The duration of DM and the degree of diabetic retinopathy (DR) were recorded for each patient.

Results: Apraclonidine instillation caused an average of 0.9 mm of mydriasis (range 0 to 4.5 mm) in DM and —0.1 mm miosis (range 0.5 to —1 mm) in control subjects ($P < 0.001$). Mydriasis of at least 1 mm was observed in 42% of DM patients. The change in PD was highly correlated with the duration of DM ($r = 0.368, P = 0.008$) and the presence of DR ($r = 0.532, P < 0.001$).

Conclusion: Apraclonidine testing, which is easy to perform and not distressing to the patient, identified PSD in nearly half of DM patients, the degree of mydriasis being correlated to the duration of DM and the presence of DR.

(J Neuro-Ophthalmol 2006;26: 25-29)

Autonomic neuropathy in diabetes mellitus (DM) often develops insidiously. Its symptoms are vague and its signs are difficult to detect on routine physical examination. The presence of cardiac autonomic neuropathy has been found to increase mortality significantly (1-3). In the early stages, autonomic and somatic peripheral neuropathy are reversible through improved glycemic control (4,5). The Diabetes Control and Complications Trial data clearly support the benefit of intensive therapy in preventing their appearance (6). Thus, screening for autonomic dysfunction would be valuable.

The pupil is a good site to obtain information about the state of diabetic autonomic neuropathy because the innervation of the pupil is exclusively autonomic and it is easily accessible for study without causing any discomfort to the patient. Infrared television pupillography is a useful device to evaluate pupillary function but expensive and not widely available (3). A more practical method is to use topical pharmacologic agents. Previous studies of topical pharmacologic testing for autonomic pupillary dysfunction have shown inconsistent results (7-11).

Apraclonidine has been found to dilate the pupil in Horner syndrome but not more than 0.5 mm in normal eyes (12,13). In an earlier study (14), we found that apraclonidine 0.5% had a sensitivity and specificity equivalent to topical cocaine in the diagnosis of Horner syndrome. It caused at least 1 mm of pupil dilation 60 minutes after instillation in eyes with cocaine-confirmed Horner syndrome, but it did not cause more than 0.5 mm dilation in any control eyes.

In this study, we used apraclonidine 0.5% to screen for pupillary sympathetic denervation (PSD) in DM and tested the strength of the correlation between PSD, the presence of diabetic retinopathy (DR), and the duration of DM.

METHODS

Patients with DM were drawn from those seeking a routine ophthalmologic examination in the ophthalmology clinic between March and June 2005. Subjects were excluded if they had an ocular pathologic condition apart from diabetic retinopathy, a contraindication to the use of $\beta$-adrenoceptor antagonists or $\alpha$-adrenoceptor agonists, previous intraocular surgery, use of contact lenses within three days before starting the study, or use of a systemic adrenergic medication within 15 days of test administration. Fifty patients with DM were recruited. Thirty healthy volunteers without DM who otherwise had the same inclusion criteria made up the control group. The evaluation of mydriasis was restricted to the right eyes in...
each group. The duration of the DM and the degree of metabolic control were recorded for each patient.

Standard ophthalmologic examinations were performed first. Baseline pupil diameters (PD) were determined to the nearest 0.5 mm using the pupil gauge on the Rosenbaum pocket vision screener in normal room lighting. The same measurements were repeated 60 minutes after instillation of one drop of apraclonidine 0.5%. After completing the apraclonidine test, fundus examinations were done under the slit-lamp and the retinal findings were recorded as diabetic retinopathy (DR) absent, background diabetic retinopathy (BDR) present, or proliferative diabetic retinopathy (PDR) present.

PD before and 60 minutes after apraclonidine instillation and the change in PD were compared in the two groups. The Independent samples t test, the x² test, and the Pearson Correlation analysis were used in the statistical analysis.

The study was approved by our institutional ethics committee and consent was taken from each patient before test administration.

RESULTS

The DM and control groups were not different with respect to age and gender (Table 1). Twenty-two patients were insulin-dependent, 26 were using oral hypoglycemic agents, and two were using dietary control alone. Fundus examination showed that 28 patients had no DR, 10 had BDR, and 12 had PDR.

The initial mean PD was significantly smaller in the DM patients than in the control subjects (P < 0.001). After instillation of apraclonidine, this situation was reversed. The average mydriasis in DM patients was 0.9 mm (range 0-4.5 mm). In the DM patients, 30 patients developed mydriasis of 0.5-4.5 mm, 18 had no change in PD, and two developed miosis. Twenty-one (42%) patients in the DM group showed a mydriatic response of 1 mm which is diagnostic for PSD (14) (Figs. 1, 2). In the control group, apraclonidine instillation caused miosis in 12 subjects, and caused slight mydriasis (up to 0.5 mm) in 5 subjects. The average change in PD among control subjects was 0 mm (range 0.5 mm mydriasis to 1 mm miosis) of miosis (Fig. 2).

In the diabetic patients, the mydriatic effect was correlated with the duration of DM (r = 0.368, P = 0.008) (Fig. 2) and with the presence of DR (r = 0.532, P < 0.001) (Fig. 3). The majority of the patients showing PSD were insulin-dependent (16/21) and had coexistent DR (17/21).

The patients displayed no adverse effects from the apraclonidine test except 1-4 mm upper lid retraction which developed in 64% of the DM patients and in 40% of the control subjects.

DISCUSSION

In the present study, we found that apraclonidine caused at least 1 mm of mydriasis in 42% of eyes with DM and in no eyes of control subjects. The degree of mydriasis in DM was correlated with the duration of diabetes and the presence of retinopathy. This finding suggests a high prevalence of PSD in DM, especially when it has been present a long time and has caused retinopathy.

Apaclonidine modulates the effect of endogenous neurotransmitters through pre-junctional and postjunctional α-receptors and would be expected to cause pupillary miosis in normal subjects (15,16). But it also has the ability to stimulate α1-adrenergic receptors with a lower efficacy than norepinephrine (12). In a study to determine its site of action in lowering intraocular pressure, apraclonidine was found to cause mydriasis in patients who had both glaucoma and Horner syndrome (12). This effect was explained by denervation hypersensitivity to apraclonidine of α1-receptors in the iris dilator muscles because of loss of normal sympathetic innervation (12,17).

Reversal of anisocoria in apraclonidine testing is now taken as a criterion for the diagnosis of Horner syndrome. However, in diabetic autonomic neuropathy, pupils are often affected bilaterally so it is not possible to use a change in anisocoria or to use the untreated eye as a control in

| Table 1. Demographic and pupillary data of the diabetes mellitus patients and control subjects |
|-----------------------------------------------|------------------|------------------|------------------|
| Demographic and pupillary data of the diabetes mellitus patients and control subjects |
| Diabetes mellitus (N = 50) | Control subjects (N = 30) | P value |
| Age (years) | 52.2 ± 13.0 | 49.9 ± 11.1 | 0.425* |
| Gender (F/M) | 29/21 | 14/16 | 0.325× |
| Baseline pupil diameter (mm) | 2.5 ± 0.5 | 3.0 ± 0.6 | <0.001* |
| Pupil diameter (mm) 60 minutes after apraclonidine 0.5% | 3.5 ± 1.2 | 2.9 ± 0.4 | 0.01* |
| Change in pupil diameter (mm) after apraclonidine | 0.9 ± 1.2 | −0.1 ± 0.4 | <0.001* |

*Independent samples t test; ×x².
FIG. 1. Bilateral pupillary sympathetic denervation in a diabetic patient demonstrated with topical apraclonidine 0.5%. A. Baseline condition shows bilateral miosis. B. There is no change in pupil size 60 minutes after instillation of cocaine 10%. C. There is bilateral mydriasis 60 minutes after instillation of apraclonidine 0.5%.

Doing pharmacological testing. To detect PSD, one must know the effects of the testing agent on normal pupils. In this study, we observed no change in the pupil diameter in the majority of control eyes.

Although we did not evaluate our patients critically in this respect, diabetic patients could have many ocular surface problems like keratoepitheliopathy, decreased corneal sensation, decreased tear film break-up time, and decreased reflex tear secretion (18-20). These changes may result in higher penetration of apraclonidine to the pupillary area in diabetic eyes as compared to healthy eyes through an impaired corneal barrier mechanism or through slow clearance from the tear film (21). The potential difference in bioavailability of apraclonidine in diabetic and healthy eyes might confound our results. However, in previous studies (12,13,22,23) the effect of topical apraclonidine on pupil size was found to be dose-independent at 0.25% to 1% and our apraclonidine concentration (0.5%) was within this range. By contrast, the intraocular pressure-lowering effect of apraclonidine appears to be dose-dependent (22-25). Although we did not apply it in our study, monitoring of intraocular pressures during testing would have been useful. Had apraclonidine lowered intraocular pressure more in diabetics, corneal permeability might have played a role.

Previous studies have shown that the response to sympathomimetic amines in healthy subjects is dependent on their age and there are no reported absolute values described for the investigated pharmacological pupil function tests (9,10). Smith and Smith (10) and Clark (9) have studied pupil denervation hypersensitivity in diabetic patients using different concentrations of phenylephrine, but these studies lacked an accurate assessment of the normal pupillary response within age groups. In those studies, the mydriatic effect of phenylephrine was highly variable and significantly correlated with the age of the patient ($r = 0.76$, $P < 0.001$ [10]; $r = 0.64$, $P < 0.001$ [9]). A similar correlation between the mydriatic effect of hydroxyamphetamine and age has also been found, but the
influence of age is less marked ($r = 0.32, P < 0.05$ [10]). An age-dependent reduction in cocaine response has been observed in previous studies (8,26). We also observed age dependency in the apraclonidine response in our study, but the strength of the correlation was less significant ($r = 0.22, P = 0.05$). Less age dependency allows us to define the limits of normal and pathologic responses more accurately, and this is an advantage of apraclonidine in screening of PSD.

Previous reports concerning pupillary sympathetic function as demonstrated with different pharmacological agents in diabetic patients are given in Table 2 (8-11). In all studies, the effect of the testing agent was compared between diabetics and age-matched controls. Smith and Smith (10) and Clark (9) reported their results as percentages of patients showing PSD. Smith and Smith (10) used phenylephrine 2% and found a prevalence of PSD equivalent to our results. Clark (9) used phenylephrine 0.5% and found a lower prevalence of PSD even though patients had a longer duration of diabetes and all had PDR. The concentration of the testing agent (0.5%) might explain the relatively low prevalence. Pittasch (11) demonstrated a significant reduction in the normal mydriatic response to cocaine 4% and pholedrine 5% in diabetic groups, but he could not demonstrate significant denervation hypersensitivity in those groups to epinephrine 1%. With its selectivity for $\alpha_1$-adrenergic receptors, phenylephrine is an effective direct adrenergic agonist for dilating the pupil by stimulating the dilator muscle. Because it stimulates both $\alpha_1$- and $\alpha_2$-adrenergic receptors, which have counteracting effects, epinephrine is a less potent mydriatic agent. Perhaps epinephrine 1% is not sensitive enough to detect denervation hypersensitivity. In performing cocaine testing, Cahill (8) could not demonstrate significant PSD in diabetics, but they had relatively mild diabetic changes.

Previous studies have established a direct correlation between the degree of cardiovascular autonomic neuropathy and the severity of retinopathy (27,28). We observed a similar correlation between PSD and the severity of retinopathy, the prevalence of PSD being 14%, 70%, and 83% in patients without DR, with BDR, and with PDR, respectively. Because we did not select our study group randomly, our results are not an accurate measure of the true prevalence of PSD in diabetics, but they do confirm that autonomic neuropathy is very common in long-term diabetics. Considering the increased risk of mortality with diabetic autonomic neuropathy, screening for it with a simple non-invasive method is valuable.

### REFERENCES


### TABLE 2. Results of reported studies of topical pharmacologic testing for pupillary sympathetic denervation in diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Duration of diabetes (average in years)</th>
<th>Topical agent</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith et al, 1983 (10)</td>
<td>34</td>
<td>15.9</td>
<td>Phenylephrine 2%</td>
<td>47% PSD</td>
</tr>
<tr>
<td>Clark, 1988 (9)</td>
<td>28</td>
<td>20.9</td>
<td>Hydroxyamphetamine 0.5%</td>
<td>Normal pupillary dilation</td>
</tr>
<tr>
<td>Cahill et al, 2001 (8)</td>
<td>31</td>
<td>Not reported</td>
<td>Phenylephrine 0.5%</td>
<td>38% PSD</td>
</tr>
<tr>
<td>Smith et al, 2002 (11)</td>
<td>141</td>
<td>14.2</td>
<td>Cocaine 4%</td>
<td>Normal pupillary dilation</td>
</tr>
<tr>
<td>Pittasch et al, 2002 (11)</td>
<td>31</td>
<td>14.2</td>
<td>Cocaine 4%</td>
<td>Reduced pupillary dilation</td>
</tr>
<tr>
<td>Current series</td>
<td>50</td>
<td>10.6</td>
<td>Epinephrine 1%</td>
<td>Normal pupillary dilation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pholedrine 5%</td>
<td>Reduced pupillary dilation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Apraclonidine 0.5%</td>
<td>42% PSD</td>
</tr>
</tbody>
</table>

PSD, pupillary sympathetic denervation.
25. Stewart WC, Laibovitz R, Horwitz B, et al. A 90-day study of the efficacy and side effects of 0.25% and 0.5% apraclonidine vs 0.5% timolol. *Arch Ophthalmol* 1996;114:1138-42.
Ischemic Optic Neuropathy Following Spine Surgery in a 16-Year-Old Patient and a Ten-Year-Old Patient

Jonathan W. Kim, MD, William L. Hills, MD, Joseph F. Rizzo, MD, Robert A. Egan, MD, and Simmons Lessell, MD

Abstract: Peri-operative ischemic optic neuropathy typically occurs in middle-aged or older patients. We report this condition in two patients aged 16 and 10 years. Only six other cases of peri-operative ischemic optic neuropathy have been reported in patients aged less than 30 years, all but one occurring after spinal surgery. Although the visual prognosis appears to be more favorable in younger patients, the pathogenesis of this rare complication of surgery is likely to be the same as that affecting older individuals.

Peri-operative ischemic optic neuropathy is characterized by unilateral or bilateral visual loss following major surgical procedures such as spinal surgery, coronary artery bypass, radical neck dissection, and others (1–8). While the pathogenesis has yet to be confidently explained, surgery-related anemia and hypotension have been postulated as possible mechanisms (1–6). This potentially devastating complication typically occurs in middle-aged or older patients (2,3,9–11). It is rare for patients under the age of 30 to develop it. We report two cases occurring in young patients undergoing spinal surgery.

METHODS

A literature search of the National Library of Medicine's PubMed database was performed with the following words and word combinations: ischemic optic neuropathy, posterior ischemic optic neuropathy, post-operative visual loss, and postoperative blindness.

CASE REPORTS

Case 1

A 16-year-old girl with neuro-muscular scoliosis, dystonia, and athetosis underwent spinal fusion surgery. The patient's medical history was otherwise unremarkable and her past ocular history was notable only for moderate hyperopia.

Arthrodesis from T1 to the sacrum was performed in the prone position with neck flexion. A molded face mask was used to avoid pressure on the globes. Her preoperative hemoglobin was 14.4 gm/dl and hematocrit was 41.5%. Systolic blood pressure was 140/70 mm Hg immediately prior to the induction of anesthesia. There were no intra-operative or postoperative complications. The estimated blood loss was 4,000 mL and total duration of anesthesia was 13 hours. Intra-operative fluid replacement included 11 units of cell saver, three units of bank blood, six units of fresh frozen plasma, four units of platelets, 9 L of lactated Ringer's solution, and 2 L of normal saline. During surgery her systolic blood pressure ranged from 80–100 mm Hg systolic. The diastolic blood pressure ranged from 40–60 mm Hg except for brief periods when it was between 30–40 mm Hg. The first day after surgery, she was transfused with two units of packed red cells to maintain her hematocrit, which was 17.5% (hemoglobin 6.2 gm/dl).

On the third postoperative day, she complained of blurred vision in both eyes. She was alert and cooperative but had to be examined supine in her hospital bed. Visual acuity was hand movements OD and 20/200 OS. She could not identify any Ishihara color plates. On confrontation visual field testing, only the left superior visual field in the left eye appeared intact. There was a right relative afferent pupillary defect. There were bilateral periorbital edema and...
small ecchymoses in her right upper eyelid. Ocular motility examination revealed normal versions and alignment and no nystagmus. Dilated fundus examination showed pallid edema of both optic discs. Apart from visual loss, there were no other neurologic deficits.

Blood pressure was 95/50 mm Hg, hematocrit 24.4%, and hemoglobin 8.7 g/dl. She was transfused for the second time with two units of packed red cells and hematocrit increased to 34% the following day. A brain CT scan showed no abnormalities.

Over the ensuing weeks, she noted gradual visual improvement. Two weeks after surgery, visual acuities were finger counting OD and 20/30 OS. The right relative afferent pupillary defect was still evident. Both optic discs were pale but less edematous. Nine months after surgery, visual acuities were 5/200 OD and 20/25 OS. She could not be positioned for perimetry, but confrontation visual field testing showed extensive central and nasal depression in the right eye and depression of the lower field in the left eye. Ophthalmoscopic examination showed bilaterally pale optic discs without edema (Fig. 1).

Case 2

A ten-year-old boy with a low thoracic meningo-myelocoele and severe lumbosacral kyphosis underwent a posterior release and instrumentation. His medical history was otherwise unremarkable and his past ocular history was significant for alternating esotropia and moderate hyperopia.

Kyphectomy was performed in the prone position with the face resting in a doughnut. Preoperative hemoglobin was 13.9 g/dL and hematocrit was 40.5%. Pre-operative blood pressure immediately prior to induction of anesthesia was 130/80 mm Hg. Estimated blood loss was 3600 cc during a total of 11.5 hours of anesthesia. Intra-operative fluid replacement included 920 mL via the cell saver, four units of packed red blood cells, two units of fresh frozen plasma, 4 L lactated Ringer's solution, 5 L normal saline, and five units of cryoprecipitate. Five units of platelets were given postoperatively in the pediatric intensive care unit. During surgery the lowest blood pressure was 70/35, which persisted for one hour. Lowest intra-operative hemoglobin was 7.5 g/dL and lowest hematocrit was 21.8%. Postoperatively, he received one unit of packed red cells, raising his hemoglobin to 9.6 g/dL and hematocrit to 27.4%. However, the following morning his hemoglobin fell to 7.3 g/dL and hematocrit to 21.1%.

On the second postoperative day, his face was markedly swollen and his parents noted that he did not see normally. He confabulated during visual acuity testing and did not appear to perceive light. His pupils were non-reactive. Dilated fundus examination demonstrated normal-appearing optic discs.

Ten months later, visual acuity had improved to 20/200 in the left eye, but still no light perception (NLP) in the right eye. He demonstrated a right relative afferent pupillary defect. Both optic discs were pale.

DISCUSSION

Our two cases are presented because peri-operative ischemic optic neuropathy is so unusual in young patients. We identified only six other cases in patients aged 30 years or younger (Table 1) (2,5,11–14). Although the sample size is small, we recognize similarities between younger and older patient groups with this condition.

Spinal surgery appears to be the most common setting for patients of all ages (2,9,10,14). Including our cases, seven of the eight reported cases in patients under age 30 occurred after spinal surgery. The only exception was a 16-year-old girl with chronic renal failure and anemia.
who was noted to have optic disc pallor following total parathyroidectomy (5). As in the older patients, most of the younger patients had normal optic discs in the immediate postoperative period with disc pallor developing during the first year of follow-up.

Younger patients appear to have a better visual prognosis than do older patients. In the series of Sadda et al (9) of 28 adult patients, 44% of eyes had a final visual acuity of hand motions or worse. The recent review of Buono and Foroozan (15) of all 83 peri-operative ischemic optic neuropathy cases reported before 2004 showed that 55% of eyes had a final visual acuity of hand motions or worse. In our study of young patients, only two (17%) out of 12 eyes had hand movement perception or worse visual acuity (when measured); five (42%) out of 12 eyes had a final visual acuity of 20/30 or better. None of the young patients were identified to have vasculopathic risk factors such as hypertension, diabetes, hypercholesteremia, obesity, or a history of smoking.

Why should peri-operative ischemic optic neuropathy be less apt to affect younger patients? Part of the explanation could be that the procedures frequently implicated in peri-operative optic neuropathies are not performed as frequently in younger groups. In the review of Shapira et al (3), of 602 patients who underwent open heart operations at the Lahey Clinic, the youngest patient to develop peri-operative ischemic optic neuropathy was 54 years old. However, complex spinal surgeries, the procedure most often associated with this complication, are commonly performed in young people (16,17). Therefore, a more satisfactory explanation is that the optic nerve in young individuals is better able to withstand the ischemic insult that results from intra-operative hypotension and blood loss. Some authors have found an association between peri-operative ischemic optic neuropathy and vasculopathic and arteriosclerotic risk factors (1,4).

Because the commonly identified risk factors (chronic hypertension, smoking, diabetes mellitus, and systemic atherosclerosis) are much less prevalent in the young, this disparity may be a contributing factor.

For all demographic groups, spinal surgery is the most common setting. In the series of Sadda et al (6), 50% of patients had undergone spinal surgery. The incidence of peri-operative ischemic optic neuropathy following spinal surgery has been estimated to be as high as 0.2% (2,10,13). By comparison, the largest series of cardiac bypass patients with peri-operative ischemic optic neuropathy identified by a retrospective study showed an incidence of 0.06% during an 18-year period (3).

The risk of peri-operative ischemic optic neuropathy is reported at 1:61,000 in a general surgery population (18). There are special features of spine surgery that may predispose to this complication, including long operative times, substantial intra-operative blood loss, and deliberate hypotensive anesthesia. Prone patient positioning has also been implicated as a causative factor. Direct pressure on the globe from a badly-positioned headrest has also been cited as a factor contributing to visual loss in several published reports, although other authors have contended that direct ocular pressure would be expected to cause central retinal artery or venous occlusion rather than ischemic optic neuropathy (19-21). It is common for patients undergoing prolonged posterior fusions or multi-level laminectomies to develop postoperative facial and periorbital edema, which may indirectly elevate orbital venous pressure. Our first case did have periorbital edema and unilateral eyelid ecchymosis. A combination of local and systemic perturbations during spinal surgery may predispose the optic nerve to ischemic insult even in young individuals without vascular disease.

Although the visual prognosis appears to be more favorable in younger patients, the pathogenesis of

### TABLE 1. Reported cases of peri-operative ischemic optic neuropathy in patients aged thirty years or less

<table>
<thead>
<tr>
<th>Case no. (ref. no)</th>
<th>Age (years)</th>
<th>Sex (M/F)</th>
<th>Surgery type</th>
<th>Surgery duration (hours)</th>
<th>Blood loss (liters)</th>
<th>Lowest operative blood pressure</th>
<th>Lowest hematocrit % or hemoglobin g/dL (hours after surgery)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (13)</td>
<td>24</td>
<td>M</td>
<td>Spinal</td>
<td>&gt;5</td>
<td>?</td>
<td>80/55</td>
<td>24% (intra-operative)</td>
</tr>
<tr>
<td>2 (2)</td>
<td>27</td>
<td>F</td>
<td>Spinal</td>
<td>?</td>
<td>5.0</td>
<td>80/50</td>
<td>26% (intra-operative)</td>
</tr>
<tr>
<td>3 (11)</td>
<td>12</td>
<td>M</td>
<td>Spinal</td>
<td>6</td>
<td>2.5</td>
<td>52 (mean)</td>
<td>7.1 g/dL (intra-operative)</td>
</tr>
<tr>
<td>4 (12)</td>
<td>13</td>
<td>M</td>
<td>Spinal</td>
<td>?</td>
<td>8.0</td>
<td>7-8.0 g/dL</td>
<td>29.9% (?)?</td>
</tr>
<tr>
<td>5 (5)</td>
<td>16</td>
<td>F</td>
<td>Parathyroid</td>
<td>?</td>
<td>?</td>
<td>100/45</td>
<td>?-8.0 g/dL (intra-operative)</td>
</tr>
<tr>
<td>6 (14)</td>
<td>19</td>
<td>M</td>
<td>Spinal</td>
<td>?</td>
<td>2.7</td>
<td>?</td>
<td>29.9% (?)?</td>
</tr>
<tr>
<td>7 (our Case 1)</td>
<td>16</td>
<td>F</td>
<td>Spinal</td>
<td>13</td>
<td>4.0</td>
<td>80/30</td>
<td>18%, 8.7 g/dL (24)</td>
</tr>
<tr>
<td>8 (our Case 2)</td>
<td>10</td>
<td>M</td>
<td>Spinal</td>
<td>11.5</td>
<td>3.6</td>
<td>70/35</td>
<td>21.1%, 7.3 g/dL (24)</td>
</tr>
</tbody>
</table>

Continued
TABLE 1 (Continued). Reported cases of peri-operative ischemic optic neuropathy in patients aged thirty years or less

<table>
<thead>
<tr>
<th>Disc edema (yes/no)</th>
<th>Unilateral/bilateral (U/B)</th>
<th>Initial postoperative visual acuity (hours after surgery)</th>
<th>Final visual acuity (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>U</td>
<td>20/20 (&lt;24 h)</td>
<td>20/80 (60 m)</td>
</tr>
<tr>
<td>N</td>
<td>U</td>
<td>20/20 (48 h)</td>
<td>20/20 (?)</td>
</tr>
<tr>
<td>N</td>
<td>B</td>
<td>? (&lt;24 h)</td>
<td>Hand movements, 16/200 (12 m)</td>
</tr>
<tr>
<td>N</td>
<td>B</td>
<td>20/30, 20/400 (24 h)</td>
<td>20/20, 20/60 (48 m)</td>
</tr>
<tr>
<td>?</td>
<td>B</td>
<td>? (72 h)</td>
<td>20/30, 20/15 (18 m)</td>
</tr>
<tr>
<td>?</td>
<td>B</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Y</td>
<td>B</td>
<td>Hand movements, 20/200 (72 h)</td>
<td>5/200, 20/25 (9 m)</td>
</tr>
<tr>
<td>N</td>
<td>B</td>
<td>No light perception, OU (48 h)</td>
<td>No light perception, 20/200 (10 m)</td>
</tr>
</tbody>
</table>

peri-operative ischemic optic neuropathy is likely to be similar to that of older patients.

REFERENCES

Bilateral Visual Loss Complicating Liposuction in a Patient with Idiopathic Intracranial Hypertension

Mário Luiz Ribeiro Monteiro, MD, Frederico Castelo Moura, MD, and Leonardo Provetti Cunha, MD

Abstract: A 34-year-old obese woman developed blurred vision in both eyes soon after large-volume liposuction of the dorsum and gluteus region bilaterally associated with abdominoplasty. An ophthalmic examination revealed severe bilateral visual loss and pallid optic disc edema. The patient gave a history of transient obscurations of vision in the past. Neuroimaging studies were non-revealing, but a lumbar puncture disclosed a markedly elevated intracranial pressure. The patient was diagnosed as having had bilateral ischemic optic neuropathy superimposed on pre-existing idiopathic intracranial hypertension (IIH). Acetazolamide treatment was used. Some visual improvement occurred, and optic disc edema evolved into severe optic disc pallor. This case shows that visual loss from optic disc infarction may be a devastating complication of high-volume liposuction in patients with underlying IIH. Because liposuction is frequently performed on obese patients, physicians should screen for signs and symptoms of IIH before undertaking this procedure.

CASE REPORT

A 34-year-old woman with a history of obesity (height 1.60 m; weight 80 Kg; body mass index = 31.20) underwent liposuction of the dorsum and gluteus region bilaterally associated with abdominoplasty. Preoperatively she had the following measurements: blood pressure 110/70, pulse 72, fasting blood sugar 97 mg/dl, and hemoglobin 13.1 g/dl. During the procedure, which was performed under spinal-epidural anesthesia and sedation, 5,500 mL of fat was removed.

After surgery the patient remained somnolent for several hours, but upon awakening the following day she complained of headache and blurred vision in both eyes. She was promptly examined, but because her temperature, blood pressure (105 × 60 mm Hg), pulse rate (109/min), respiration rate (16/min), and clinical examination seemed to be within the normal range, the symptoms were initially attributed to the effects of blood loss during surgery.

Five days after surgery, we examined the patient. When questioned about previous ocular symptoms, she reported that several months before surgery, she had started experiencing transient visual obscurations in both eyes, each episode lasting a few seconds and usually triggered by postural changes such as bending over or rising. She had not consulted an ophthalmologist about these symptoms and denied having headaches or double vision. Her most recent eye examination had been performed ten years previously and was reported as unremarkable.

General clinical and neurologic examinations were within normal limits. Best-corrected visual acuity was hand movements OU. External eye examination, extraocular movements, and slit lamp examination were normal. Pupils were equal in size and reacted sluggishly to light, but no relative afferent pupillary defect was observed. The intraocular pressure by applanation was 16 mm Hg bilaterally. Ophthalmoscopy showed bilateral pallid optic disc edema with a splinter hemorrhage OD (Fig. 1). The remainder of the fundus examination was normal.

Brain MRI and magnetic resonance venography (MRV) were normal. Lumbar puncture revealed clear and colorless cerebrospinal fluid (CSF) with an opening pressure of 59 cm H2O. The CSF formula was normal.
FIG. 1. Two weeks after liposuction surgery, bilateral pallid optic disc edema is present.

FIG. 2. Two weeks after surgery, Goldmann visual fields show residual islands of vision in the temporal fields bilaterally.

FIG. 3. Six weeks after surgery, bilateral optic disc pallor is present together with a ring of gliosis around the optic discs indicating that papilledema had been long-standing.
She received a diagnosis of IIH and was treated with acetazolamide 250 mg orally QID and dexamethasone orally 4 mg/d. Headaches decreased and visual acuity improved to finger counting at 20 cm OU. Goldmann perimetry showed only a residual island of vision in the temporal field with V/4e and I/4e isopters bilaterally (Fig. 2).

A second lumbar puncture on the ninth day of treatment revealed an opening pressure of 16 cm H2O. Medical treatment was maintained, and six weeks after surgery, visual acuity had improved to finger counting OD and 20/200 OS. Papillodema had diminished and was eventually replaced by bilateral optic disc pallor OU. A peripapillary hypo-pigmented ring suggested long-standing papilledema (Fig. 3). Dexamethasone was eventually discontinued and the acetazolamide dose reduced to 500 mg/d. A third lumbar puncture performed two months after surgery disclosed an opening pressure of 20 cm H2O.

DISCUSSION

Liposuction surgery is a procedure that can help sculpt the body by removing unwanted fat from specific areas, including the abdomen, hips, buttocks, thighs, knees, upper arms, chin, cheeks, and neck. It is today the most commonly performed aesthetic procedure worldwide (1,2). Although considered a safe procedure, local and systemic adverse outcomes, such as pulmonary fat embolism, infection, pituitary apoplexy, deep venous thrombosis, fluid overload, and death have been reported (10–12). The safety of liposuction has improved since the introduction of the tumescent technique, designed to remove approximately 1,500 mL of localized fat for cosmetic purposes in non-obese subjects. However, technical improvements have led to an increase in the volume removed by way of liposuction, and unfortunately the procedure is now frequently used in obese patients.

Large-volume liposuction (>3000 mL of aspirate) may be associated with a relatively high rate of morbidity and mortality due to hemodynamic complications. Patients are exposed to prolonged interventions, fluid shifts, and infusion of high doses of epinephrine and lidocaine added to the wetting solution for their analgesic and hemostatic effects. Increased intraoperative cardiac index, heart rate, and mean pulmonary arterial pressure associated with intraoperative low body temperatures have been documented (1). After surgery, an increased cardiac work has been observed in patients with high-volume liposuction possibly associated with epinephrine administration and hemodilution related to the procedure (1). Hemodilution in the postoperative period is probably the result of fluid shift from the operative field and blood loss during surgery given that 25% to 30% of the aspirate may consist of blood (11,12).

Visual loss after liposuction has been reported only three times (7–9). Minagar et al (7) described a 47-year-old woman who underwent liposuction of the abdomen, thighs, and arms and developed postoperative hypotension and anemia. Visual loss developed in the OD on the second postoperative day, and pallid optic disc edema was noted upon ophthalmoscopy. The left optic disc had a normalized physiologic cup. Brain MRI and magnetic resonance angiography were normal. The authors believed that the patient had had postoperative anterior ischemic optic neuropathy (AION) precipitated by acute blood loss and hypotension. Sighatullah et al (9) reported a very similar patient suffering from unilateral AION developing two days after liposuction, when her hematocrit was only 23.5%. Foroozan and Varon (8) reported a patient who developed bilateral AION after high-volume liposuction. The patient also developed pulmonary embolism and dural venous sinus thrombosis. The examination disclosed bilateral pallid optic disc edema and hemorrhage. Transverse sinus thrombosis was suggested by MRV but no intracranial pressure measurements were reported. Severe anemia with a hemoglobin of 7.0 g/dl and hematocrit of 21.6% was documented in the postoperative period. In these three cases, visual loss was most likely precipitated by severe postoperative anemia resulting in AION.

Our patient differs from these previously reported cases in that her visual loss was due to bilateral AION in the setting of chronic papilledema in IIH. Hypotension owing to large-volume liposuction likely led to infarction in a disc made vulnerable by being crowded and under increased CSF pressure.

Although anemia was not documented in blood samples drawn nine days after surgery, we believe red blood cell loss, transient hemodilution, and hypotension may have contributed to visual loss. Since liposuction is frequently considered in the treatment of obese patients and obesity is a known predisposing factor for IIH, physicians should consider inquiring about transient visual obscurations and screening for papilledema before proceeding with liposuction on such patients.

REFERENCES

Pitfalls in the Diagnosis of Mitochondrial Encephalopathy with Lactic Acidosis and Stroke-Like Episodes

Iris Ben-Bassat Mizrachi, MD, Diana Gomez-Hassan, MD, PhD, Mila Blaivas, MD, PhD, and Jonathan D. Trobe, MD

Abstract: We describe a patient with genetically- and biochemically-proven mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) who was initially misdiagnosed as having had multiple ischemic strokes in part because the clinical presentation appeared to be acute, the MRI of lesions showed restricted diffusion, and the brain biopsy showed features suggestive of stroke. This report emphasizes the pitfalls in the diagnosis of MELAS and points out the similarities and differences between MELAS and ischemic stroke.

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) has clinical, imaging, and brain biopsy features that resemble those of ischemic stroke. We report a patient with genetically- and biochemically-proven MELAS who was initially misdiagnosed as having had ischemic stroke due to an acute neurologic decline and an MRI scan and brain biopsy interpreted as most consistent with ischemic stroke. We call attention to features that promote diagnostic confusion between MELAS and ischemic stroke.

CASE REPORT

A 34-year-old man was hospitalized in July 2004 because of fatigue and weakness of the left side of the body for several days and increased lethargy and confusion in the past few weeks. He had a history of insulin-dependent diabetes mellitus, bilateral sensorineural hearing loss, and abuse of alcohol, cocaine, and marijuana.

General physical examination demonstrated short stature and normal vital signs. He was alert and fully oriented. Neurologic examination was otherwise normal apart from reduced strength in the left upper and both lower extremities and diminished deep tendon reflexes throughout. MRI demonstrated a large area of high signal on T2-weighted and FLAIR sequences that involved the right posterior frontal, temporal, parietal, and occipital lobes with midline and uncal shift due to mass effect. Diffusion-weighted images (DWIs) showed a small area of high signal in the occipital region interpreted as T2 "shine-through" rather than restricted diffusion since the apparent diffusion coefficient (ADC) value was normal. The regions of signal abnormality extended across vascular boundaries (Fig. 1, A–C). T1-weighted imaging showed high signal in the basal ganglia bilaterally (Fig. 1D). The imaging findings were interpreted as consistent with subacute infarction albeit atypical as the signal abnormalities transgressed the domain of a single circumflex cerebral artery. The basal ganglia T1 high signal was attributed to mineralization. Electroencephalography (EEG) demonstrated bilateral generalized background slowing suggestive of diffuse encephalopathy and profound slowing involving the right hemisphere.

The tentative clinical diagnosis was subacute ischemic stroke attributed to diabetes and substance abuse. However, because of his young age, the bilaterality of the EEG abnormalities, and the fact that MRI abnormalities extended beyond a single arterial domain, he underwent brain biopsy.

Brain biopsy demonstrated multiple small confluent regions of recent parenchymal damage that contained proliferating small vessels, macrophages, perivascular edema with lymphocytic infiltration and hemosiderin deposits, ischemic neurons, and reactive astrocytes (Fig. 2). These findings were interpreted as consistent with ischemic infarct. But because they were not entirely specific for infarct, he was treated for herpes simplex encephalitis with intravenous acyclovir for ten days. After discharge to a rehabilitation facility, he was temporarily lost to follow-up.

Four months later, he was re-admitted for headache, vomiting, visual deterioration, and confusion developing...
FIG. 1. A-D. MRIs from the first admission, July 2004, weeks after onset of left-sided weakness, lethargy, and confusion. A. Axial T2 image shows cortical thickening and increased signal in subjacent white matter of the right temporo-parieto-occipital region. B. Axial FLAIR image shows the same findings. C. Diffusion-weighted image (DWI) shows a small area of high signal in the occipital region interpreted as T2 “shine-through” rather than restricted diffusion (apparent diffusion coefficient value was normal). D. Axial pre-contrast T1 shows high signal in the caudate and putamen bilaterally. E-H. MRIs from the second admission, November 2004, days after development of acute confusion and visual loss. E. Axial T2 image shows residual high signal in the right posterior cerebral hemisphere with striking new cortical thickening and subjacent white matter high signal in the left temporo-occipital region. F. Axial FLAIR image shows the same findings. G. DWI shows large area of high signal in the same location interpreted as restricted diffusion. H. Axial pre-contrast T1 again shows high signal in the caudate and putamen bilaterally. I-K. MRIs from second admission, December 2004. I. Axial T2 image shows lessening of high signal in previously affected region. J. Axial FLAIR shows the same findings. K. DWI shows regression of restricted diffusion. L. Non-contrast CT from the second admission, November 2004. It shows high attenuation in the basal ganglia bilaterally. There is a large area of low attenuation in the posterior cerebral hemispheres bilaterally reflecting tissue damage there.
over several days. He was disoriented to time and place, did not follow simple commands, had slow and echolalic speech, and demonstrated combative behavior. He was too inattentive to cooperate adequately with complex neurological assessment, but he appeared to have visual acuity no better than finger counting OU and he did not blink to threat. He would not cooperate for confrontation visual field testing. Extraocular movements and alignment were normal, pupils were round and reactive without relative afferent pupillary defect, and fundi were normal. He appeared to have normal strength. Deep tendon reflexes were decreased in all extremities.

MRI demonstrated a new left parieto-temporo-occipital lesion with confluent high T2-weighted and FLAIR signal and restricted diffusion. There was right parieto-temporo-occipital encephalomalacia without restricted diffusion (Fig. 1, E–G). T1-weighted imaging again showed high signal in the basal ganglia bilaterally which was present on a non-contrast CT (Fig. 1, H–I). The new imaging abnormalities were considered consistent with acute ischemia in the left cerebral hemisphere attributable to small vessel disease. However, the possibility of mitochondrial disease was now raised, principally because of the basal ganglia signal abnormality. A cerebral angiogram was normal, showing no evidence of vasculitis. A work-up for hypercoagulability and an embolic source was negative.

More attention was now paid to the bilateral sensorineural hearing loss, short stature, history of diabetes mellitus, and the fact that imaging abnormalities crossed vascular boundaries. In aggregate, these findings led to a suspicion of MELAS. Lactic acid was found to be elevated at 3.9 mmol/liter (normal 0.5–2.2 mmol/liter) in blood and 4.8 mmol/liter in the cerebrospinal fluid (normal <3 mmol/liter), which had an otherwise normal formula. Vastus lateralis muscle needle biopsy showed numerous ragged red fibers (Fig. 3). Mitochondrial DNA analysis of a peripheral blood leukocyte sample yielded an A-to-G point mutation at base pair 3243, confirming the diagnosis of MELAS.

A brain MRI performed three weeks after the second hospital admission demonstrated unchanged T2-weighted and FLAIR high signal in the same region; these lesions no longer had restricted diffusion (Fig. 1, J–K).

**DISCUSSION**

We report a case with a classical clinical presentation of MELAS that was initially misdiagnosed as ischemic stroke. The misdiagnosis was based on three features: 1) a clinical course consisting of rapid decline in neurological function, 2) MRI abnormalities considered compatible with ischemic stroke, and 3) brain biopsy considered compatible with ischemic stroke.

**Clinical Course**

On the first admission, our patient presented with evolving symptoms over several weeks. Physicians dismissed the protracted history in favor of the striking imaging findings to reach a diagnosis of stroke. On the second admission, four months later, the presentation was much more acute, leading to an even stronger misimpression of stroke.

The tempo of clinical manifestations in MELAS can sometimes lead to a misdiagnosis of stroke. Symptoms are usually subacute in onset but may be as acute as is seen in ischemic stroke (hence the term “stroke-like” in MELAS).
In 110 patients with MELAS, Hirano et al (1,2) reported acute stroke-like episodes in 14 patients (13%). Protracted symptoms tend to precede the acute neurologic decline, but they are often overlooked. Among 40 patients with MELAS, Goto et al (3) found that muscle weakness, mental retardation, headache, short stature, and vomiting were present in 50% of patients before the acute stroke-like episodes, but that these manifestations were not sufficiently severe to bring the patient to medical attention.

MRI Scan

The MRI differentiation between MELAS and ischemic stroke has been a source of confusion. Four distinguishing features of MELAS have been described, but none is entirely specific.

Cortical Gray Matter-Based Signal Abnormalities. Cortical gray matter signal abnormalities are reported to be based more common in MELAS than in ischemic stroke. For example, Matthews et al (4) described MRI lesions in three MELAS patients that were confined to the cortex and adjacent white matter with relative sparing of the deep white matter. The authors suggested that the gray matter, which is metabolically more active, is more vulnerable than the white matter. In 13 of 14 autopsies of MELAS patients, Hirano et al (1,2) found that the lesions were located in the cortex and subcortical white matter with relative sparing of the deep white matter. However, there are also several reports describing predominant involvement of the white matter (5,6). In four patients with MELAS, Barkovich et al (7) found that two had mainly white matter disease with relative sparing of the deep white matter. Thus, the presence of predominantly white matter signal abnormalities should not be construed as excluding MELAS.

Lack of Restricted Diffusion. A normal ADC, implying lack of restricted diffusion, is said to occur in MELAS but not in acute stroke, which characteristically shows a low ADC. Several reports (8–13) describe cases of MELAS with a normal or elevated ADC. This differentiating point has become such accepted dogma that it appears in review articles and text books (14), as evidenced by the following comment: "...increased ADC values in the appropriate clinical setting must raise suspicion of MELAS" (15). However, Wang et al (16) have reported a low ADC in a patient with MELAS on an MRI done five days after presentation. Follow-up MRI six days later continued to demonstrate a low ADC, but a scan performed 189 days later showed a normal ADC.

Our patient did not have restricted diffusion on MRI during the first hospital admission, but did have restricted diffusion on MRI during the second hospital admission. How can we reconcile these differing findings? On the first admission, the imaging study was performed several weeks after the onset of symptoms, too late to show restricted diffusion. On the second admission, the MRI was performed within days of acute neurological decline. Three weeks later, MRI showed disappearance of the restricted diffusion and normalization of the ADC value (Fig.1, I–K), exactly as would be seen in ischemic stroke. Thus, the literature claiming that the pattern of restricted diffusion is different in acute stroke and MELAS is misleading. We believe our case to be the first to demonstrate that the evolution of restricted diffusion occurs in MELAS just as it does in ischemic stroke, except that in MELAS, the time of onset of neuronal death is difficult to determine. We presume that previously reported cases that failed to show restricted diffusion had their MRIs performed too late to show it.

Signal Abnormalities Extending across Vascular Domains. Unlike most ischemic stroke, MELAS signal abnormalities are generally not restricted to traditional vascular territories. But combined territorial and watershed ischemic strokes may certainly extend across traditional territorial domains of vascular supply. Indeed, clinicians interpreted that our patient's MRI findings were consistent with such a combination.

High T1 and Low T2 Signal in the Basal Ganglia. Such signal abnormalities, located predominantly in the globus pallidus and caudate nucleus, are detected in 43%–53% of patients with MELAS (2). Histopathologically, calcium deposits are found in these tissues in 65% (2,14,17), generally within small blood vessels (1,17–19). Electron microscopic analysis of the calcified small vessels of the globus pallidus in one MELAS autopsy revealed increased calcium, phosphorus, and iron (20). As seen in our patient, these signal abnormalities may be explained by shortening of the T1 relaxation time of the hydrogen protons next to the surface of calcium crystals (21–23). Such signal abnormalities do not typically occur in ischemic stroke, which rarely targets these tissues bilaterally. Instead, they reflect intracellular energy failure from anoxia, toxins, electrolyte disturbances, nutritional disorders, and genetic disorders affecting oxidative phosphorylation (24). In essence, mineralization occurs as a marker of metabolic cell death (dystrophic mineralization). Such signal changes on CT and MRI may also occur as an age-related phenomenon. They were found in 0.36%–0.6% of 5,000 (25) and 12,000 (26) CT scans but only in the globus pallidus. Thus, such signal changes found in patients under the age of 40 or outside the globus pallidus should not be dismissed. Our patient demonstrated hyperintense T1 signal and low T2 signal on all MRI scans, but on the first MRI scan these characteristics were considered incidental and were upstaged by the overwhelming signal abnormalities in the cerebral white and cortical gray matter.
Magnetic resonance spectroscopy (MRS) may offer an adjunct to MRI in differentiating MELAS from stroke. Reflecting the metabolic consequence of disruption of oxidative phosphorylation, the MRS findings in MELAS include markedly elevated lactate and reduced N-acetylaspartate (NAA), glutamate, and myo-inositol (27,28). MRS can also demonstrate the presence of elevated lactate in normal-appearing brain parenchyma of MELAS patients (6,28). The MRS changes in acute ischemic stroke are similar to those of MELAS, consisting of elevated lactate and reduced NAA due to lack of perfusion and conversion from oxidative to anaerobic metabolism. In ischemic stroke, however, these MRS changes will be restricted to the ischemic region and would not, as in MELAS, appear in a normal-appearing brain (29).

Brain Biopsy

The third pitfall in our case was the brain biopsy, which was interpreted as consistent with an ischemic infarct. However, the histopathology of mitochondrial encephalomyopathies resembles that of ischemic infarct in showing gross swelling due to edema in the acute stage and cystic changes in the chronic stage. Microscopically, the acute/subacute stages display neuronal eosinophilia, reactive astrocytosis, infiltration of macrophages and lymphocytes, cytotoxic and vasogenic edema, and proliferation of small blood vessels (17). These findings are non-specific results of reduced oxygen, blood flow, or glucose, and malfunction of oxidative phosphorylation. In 10 of 14 MELAS autopsies, Hirano et al (2) found changes identical to those seen in ischemic infarcts. However, two features that distinguished MELAS from ischemic stroke were calcification of the basal ganglia, present in 11 of the 14 cases, and ragged red muscle fibers, present in all 12 cases in which muscles were examined. In seven MELAS autopsies, Tanahashi et al (30) reported findings similar to those of Hirano et al (2).

In making the diagnosis of MELAS, the clinician should be aware of the pitfalls that suggest stroke. The clinical course is usually subacute but may be acute, the MRI may show restricted diffusion if performed within the first week of onset of new symptoms, and the brain biopsy may show changes identical to those of stroke. Even so, the diagnosis should be suspected in a patient who is not stroke-prone and has short stature, sensorineural hearing loss, and an MRI that shows altered signal extending across vascular boundaries and T1 high signal in the deep cerebral gray matter.

REFERENCES

Traumatic Optic Neuropathy Caused by Blunt Injury to the Inferior Orbital Rim

Tomo Nishi, MD, Tetsuo Ueda, MD, Eiichi Yukawa, MD, Takeo Ohta, MD, and Yoshiaki Hara, MD

Abstract: A 48-year-old woman was struck on the right inferior orbital rim by a gardening device and immediately developed complete visual loss in the right eye. Clinical and imaging evaluations failed to disclose any damage to the globe or optic nerve or to their nearby soft tissues and bones. Within months, ipsilateral optic disc pallor, a nerve fiber bundle visual field defect, and a persistently subnormal visual acuity developed. We attribute the visual loss to indirect optic nerve injury. To our knowledge, blunt injury to the inferior orbital rim has not been reported as a cause of this phenomenon.

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Traumatic optic neuropathy (TON) is most commonly caused by indirect injury through a blow to the superior orbital rim or brow that is transmitted through the bone to the optic canal where it contuses the optic nerve (1). We report a patient who developed optic nerve damage from a blow to the inferior orbital rim, a phenomenon not previously described.

CASE REPORT

A 48-year-old woman presented with sudden visual loss in the right eye. She had been weeding a garden and bending down when she was accidentally struck on the right inferior orbital rim by the obtuse top of a 10 mm diameter and 80 cm length stake used to support the growth of plants. The stake was made of steel and colored green so that it was difficult to recognize in the fields. She immediately noted rapid visual loss in the right eye and went to the hospital.

On initial examination, visual acuity was no light perception (NLP) OD and 20/15 OS. Intraocular pressures were 16 mmHg OD and 17 mmHg OS. In dim illumination, the pupil in the right eye measured 5 mm and the pupil in the left eye measured 3 mm. Both pupils were round; the pupil in the right eye did not react to direct light whereas the pupil in the left eye reacted normally; a relative afferent pupillary defect was present in the right eye. The anterior segment, ocular media, and fundus examinations were normal in both eyes (Fig. 1). There was a superficial skin laceration of the lower lid at the orbital margin.

Fluorescein angiography and indocyanine green angiography showed no delays in circulation time between arm and retina or between arm and choroid and no leakage from the optic discs or retinal blood vessels. Plain x-ray studies (Waters, semi-Waters, Rhese methods) and CT of the head and orbits did not show any fractures (Fig. 2). MRI showed no abnormalities of the optic nerves; neither optic nerve enhanced with contrast dye.

As a result of these findings, we suspected TON. Therefore, we instituted a three-day course of intravenous methylprednisolone 1000 mg/d followed by a tapering dose of oral prednisone over 11 days. One week after injury, visual acuity had improved to 20/200 in the right eye; one year after injury, it had improved to 20/100. The optic disc in the right eye had become diffusely pale at three months after injury while the optic disc in the left eye remained normal in appearance (Fig. 1). Goldmann perimetry

FIG. 1. One day after blunt trauma to the right orbit, the right optic disc appears normal (left panel). Three months after injury, the right optic disc is diffusely pale (right panel).
FIG. 2. Axial CT at the time of injury shows no soft tissue or bone abnormalities.

showed a superior nerve fiber bundle defect at three months after the injury (Fig. 3).

DISCUSSION

Most indirect injury to the optic nerve occurs from blows to the superior orbital rim or brow (1). Our case is unusual in that the blunt trauma appeared to affect the inferior orbital rim. We have excluded direct trauma of the optic nerve because: 1) the lid laceration in our patient was too superficial to suspect a penetrating injury with direct force on the optic nerve; 2) there were no indications of blunt injury to the globe itself; and 3) there was no imaging evidence of damage to the optic nerve or orbital soft tissues. However, the optic nerve was the site of damage, as it eventually became pale, a nerve fiber bundle visual defect appeared, and no abnormalities of the retina were found.

We therefore assume that our patient suffered indirect injury to the optic nerve with a mechanism similar to that proposed for conventional indirect injury to the optic nerve. We have encountered no comparable reported cases except one by Laurence et al (2), in which injury to the nasal conjunctiva was associated with TON. The authors reported that the force of a merchandise display hook striking the left orbit nasally rotated the globe and caused optic nerve damage by stretching. As hypothesized by Leino (3), sudden stretching and tearing combined with compression and hemorrhage might be a major mechanism in optic nerve injury. The optic nerve is vulnerable to sudden stretching even without energetic co-forces or fractures. Sanborn et al (4) surmised that at least two mechanisms might be responsible for evulsion of the optic nerve after a non-penetrating injury (4). First, when struck by an
object, the globe is displaced into the orbit, and intraocular pressure rises sharply, forcing the optic nerve away from the globe. Second, high intraorbital pressure forces the globe forward. A tethering effect results in separation of the optic nerve from the globe. We have considered a similar mechanism in our case. Furthermore, since the superior portion of the optic nerve is most tightly bound within the canal, the inferior pial vessels are considered to be most susceptible to shearing forces (1). Based on this hypothesis, the superior visual field would be lost, as in our case. Thus, a combination of optic nerve rotation and circulatory loss might conspire to cause visual loss.

REFERENCES

Magnetic Resonance Imaging of Third Cranial Nerve Palsy and Trigeminal Sensory Loss Caused by Herpes Zoster

Susannah V. Quisling, MD, Vinay A. Shah, MD, Ho K. Lee, MD, PhD, Bruno Policeni, MD, Wendy R. K. Smoker, MD, FACR, Coleman Martin, MD, and Andrew G. Lee, MD

Abstract: A 44-year-old man with right-sided herpes zoster ophthalmicus (HZO) developed ipsilateral third and sixth cranial nerve palsies and first-division trigeminal (fifth cranial nerve) sensory loss. MRI revealed contrast enhancement of the cisternal and cavernous portions of the third cranial nerve and high signal on a FLAIR sequence within the ipsilateral medulla at the presumed location of the trigeminal nucleus and tract. To our knowledge, this is the first report of the combination of these imaging findings in HZO.

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examination showed a few punctuate epithelial erosions but no active uveitis OD. Intraocular pressure measurements were 10 mm Hg OD and 13 mm Hg OS. Other aspects of the ophthalmologic and neurologic examinations were normal.

Brain MRI revealed enhancement and thickening of the cisternal and cavernous portions of the right third cranial nerve (Fig. 1A). FLAIR MRI demonstrated high signal intensity in the right posterolateral medulla consistent with presumed involvement of the trigeminal nucleus and tract (Fig. 1B). The clinical and imaging findings were attributed to herpes zoster. Cerebrospinal fluid (CSF) analysis demonstrated 30 white blood cells/mm³, a protein 56 mg/dl, and glucose 107 mg/dl. The patient was treated with intravenous acyclovir 660 mg TID for ten days and intravenous methylprednisolone 1 g/d for three days. He was then treated with oral acyclovir 500 mg 3× per day for two months and oral prednisone in a tapering dose over several weeks. The MRI was not repeated but at last follow-up examination three months after onset, he had no uveitis, a 9 prism diopter right hypertropia, and only 2 mm of right upper lid ptosis.

HZO-related ophthalmoplegia is uncommon but can affect cranial nerves III, IV, or V₁ (1,2). Most patients are over the age of 50 years. The ophthalmoplegia usually occurs one to two weeks after the rash. The reported cases of HZO ophthalmoplegia have demonstrated abnormal enhancement of the orbit, cranial nerves, optic nerve, and pons (3,4). To our knowledge, this is the first case of HZO-associated ophthalmoplegia with enhancement of the third cranial nerve and FLAIR MRI abnormalities involving the trigeminal nucleus in the medulla. Other authors, however, have reported the T2 signal abnormality in the medulla with or without enhancement of the trigeminal nerve. Koudo et al (9) reported a 64-year-old woman with herpes zoster meningocerebralitis followed by involvement of cranial nerves IX, X, XI. On the T2-weighted MRI, there was a high-signal lesion in the left dorsal part of the medulla. Haanpää et al (10) reviewed brainstem MRI findings of 16 cases of uncomplicated herpes zoster (12 trigeminal and four cervical) and reported a focal T2-weighted hyperintensity in nine patients, most often within the trigeminal nuclear complex, including the spinal trigeminal nucleus in four cases. Three cases had trigeminal nerve enhancement. Nagane et al (11) reported a case of right second-division trigeminal zoster with right upper cervical neuralgia and facial palsy from zoster sine herpete. The brainstem MRI revealed T2-weighted hyperintensity in the right spinal trigeminal nucleus from the lower pons to C2. The spread of the HZV to the spinal trigeminal nucleus and tract has been hypothesized to be due to centripetal migration from the gasserian ganglion (5).

There are no high-quality data to support treatment of HZO-associated ophthalmoplegia. Systemic antiviral medication and corticosteroids have been recommended, however. The ophthalmoplegia typically shows significant improvement or resolution within several months (6). Rarely, patients may have severe neurologic complications of HZO, including delayed contralateral hemiplegia (7,8). Our patient experienced gradual improvement over three months after treatment with intravenous and oral acyclovir and corticosteroids.

REFERENCES

Rapidly Progressive Bilateral Ophthalmoplegia and Enlarging Sellar Mass Caused by Amelanotic Melanoma

Saiju Jacob, MD, MRCP, Eleanor Pye, MRCP, Majed Hbahbih, MRCP, Nicholas Messios, DMRD, FRCP, and Yusuf A. Rajabally, MD

Abstract: A 63-year-old woman with diplopia and bilateral ptosis underwent brain MRI that showed a pituitary mass with signal characteristics suggestive of adenoma. Within one week she had developed nearly complete bilateral ophthalmoplegia. A repeat MRI showed extension of the mass into both cavernous sinuses. Hypophysectomy disclosed an amelanotic melanoma. Extensive search for a primary source was unsuccessful. Despite local radiation treatment, the tumor continued to grow and the patient became blind and died within several months of diagnosis. There are seven reported cases of melanoma arising primarily in the sella turcica. Two cases of metastatic melanoma to the cavernous sinuses have been reported. Amelanotic melanoma has not been reported as a cause of cavernous sinus syndrome.

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A 63-year-old woman had a four-week history of headache and a one-week history of diplopia and left upper lid ptosis. Her past medical history was unrevealing. Examination confirmed left upper lid ptosis with normal eye movements, alignment, pupillary size, and reactions.

MRI scan showed enlargement of the pituitary gland to 11 mm with a non-enhancing area on its left side measuring 4 × 5 mm consistent with macroadenoma (Fig. 1, A–B). No other intracranial abnormality was macroscopically detected. When examined two weeks later, she had no horizontal eye movements and markedly reduced vertical movements in the left eye. Repeat MRI (Fig. 1C) showed that the enhancing lesion arising from the pituitary gland had extended into the cavernous sinuses bilaterally. Investigations for infection, inflammation, autoantibodies, tumor markers, endocrine function, and cerebrospinal fluid abnormalities were unremarkable.

Transphenoidal hypophysectomy with debulking of the tumor revealed highly neoplastic cells in the adenohypophysis. Tumor markers for epithelial, germ cell, neuroendocrine, primitive neuroectodermal tumors, and lymphoma were negative. Immunoreactivity for S100 Melan-A and HMB45 was later identified. No pigment was seen on staining with hematoxylin and eosin; Masson Fontana stain showed only very occasional focal pigmentation. The histologic diagnosis was amelanotic melanoma.

Within six weeks of admission, she had lost all vision in the left eye, and later in the right eye. Repeat MRI scans during this period showed a rapidly enlarging tumor invading both cavernous sinuses (Fig. 1, C–D). Detailed dermatological and ophthalmological examinations with CT scanning of the chest, abdomen, and pelvis failed to demonstrate a primary source or evidence of disease activity elsewhere.

A six-week course of fractionated radiotherapy was administered to the sellar region. At that point, the patient was able to recognize shapes. Unfortunately, all vision was lost again within weeks. She died shortly thereafter. No autopsy was performed.

Intracranial malignant melanomas have generally arisen as metastases from primary lesions outside the cranial cavity. Only 1% of all newly-diagnosed melanomas are primary to the intracranial space (1). Melanomas arising primarily from the sella turcica is exceedingly rare, only seven cases having been reported (2–8). One case report of a cavernous sinus syndrome secondary to metastatic malignant melanoma has been published in the English literature (9). This patient presented with a cavernous sinus syndrome, the initial MRI being normal. Later he was found to have a metastatic malignant melanoma from a lymph node biopsy. Subsequent MRI showed an enhancing lesion in the region of the cavernous sinus presumably due to metastatic disease. There is a similar case report published in the Japanese literature (10). Sellar amelanotic melanoma has not been reported as a cause of cavernous sinus syndrome.

Our case points out that MRI cannot differentiate initially between the more common pituitary adenoma and unusual tumors such as melanoma. Had there been more pigment in the tumor, areas of high T1 signal and low T2 signal corresponding to the pigment might have suggested the diagnosis (11). The rapidly progressive bilateral ophthalmoplegia and imaging evidence of tumor growth logically gave rise to the mistaken notion of a malignant pituitary adenoma. Pituitary abscess would have been a clinical consideration but imaging features were not consistent with this diagnosis. Given the rapid demise of our patient, we presume that she had occult metastatic disease undetected with CT surveillance. Positron emission tomography may have been more sensitive.

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Diffusion Tensor Magnetic Resonance Imaging

Vikas Gulani, MD, PhD, and Pia C. Sundgren, MD, PhD

Abstract: Molecular diffusion plays an important role in many biologic phenomena. The ability to study diffusion, therefore, is extremely useful in physiology and medicine. MRI offers a non-invasive window to diffusion, particularly water self-diffusion. MRI techniques, which provide diffusion sensitivity or quantitation (diffusion tensor MRI [DTI]), have found widespread application in neuroscience and medicine, including the evaluation of stroke, brain development, tumor imaging, and demyelinating disorders. We discuss the tensor nature of diffusion and provide an overview of how DTI offers unique information on tissue organization, water mobility, and disease states, particularly those of neuro-ophthalmologic interest.

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Diffusion tensor imaging (DTI) refers to a set of MRI techniques designed to provide information about water mobility (diffusion) and tissue microstructure and organization in relation to directionality of diffusion. In general, and particularly in white matter, water mobility is not equal in all directions (isotropic) but greater in one direction than another. Therefore, diffusion in white matter is described as anisotropic. This anisotropy means that diffusion is characterized, not by a single coefficient, but by a second-order symmetric tensor of six unique elements or diffusivities requiring multiple measurements for complete determination. Once these six diffusion coefficients have been obtained, the degree of mobility of water protons in the system can be determined with an average principal diffusivity. The degree of anisotropy of this mobility can be determined by calculating anisotropy indices such as fractional anisotropy (FA). Anisotropy indices give information about tissue organization, degree of myelination, and water mobility, and serve to complement a traditional anatomic MRI examination (Fig. 1). While some anatomic information is included in all four images of Figure 1, the traditional T2-weighted image contains no information about mobility that the apparent diffusion coefficient (ADC) map provides. The FA and color-coded FA maps provide information about white matter organization and direction of maximal water mobility. (For a more detailed introduction to DTI techniques, refer to the Appendix).

The structural and organizational information contained in a DTI examination is used as a complement to a traditional anatomic imaging examination. In the short period since its introduction as an experimental technique in 1994, DTI has already been applied to a wide range of clinically relevant areas, including fiber tract mapping, brain maturation, ischemia, demyelinating disease, and tumor imaging.

APPLICATIONS OF DIFFUSION TENSOR IMAGING

Fiber Tract Mapping

Much effort has been exerted in finding single image display schemes for the information within the diffusion tensor, including voxel-wise three-dimensional display forms such as the diffusion ellipsoid (1) and various color schemes (2). These techniques attempt to incorporate the anisotropy information contained in the eigenvalues and scalar invariants such as FA in the magnitude of the display and the directional information contained in the eigenvectors in the color scheme used (Fig. 1). Pushing this directionality information one step further, several groups have accomplished fiber tract mapping using DTI (3–8). The local fiber orientation in each voxel is determined via DTI, and then voxels are connected to each other, starting at a seed point and propagating a tract by mathematically connecting the adjacent voxels based on information gleaned from the magnitude and directionality of diffusion anisotropy. A detailed review of these fiber tracking methods is beyond the scope of this article. An excellent starting point for understanding tractography has been provided by Mori and van Zijl (9).

These methods provide an unprecedented opportunity to study brain connectivity in vivo. A particularly interesting future possibility is the combination of tractography with blood oxygenation level-dependent (BOLD) or perfusion-based functional MRI (fMRI) to...
obtain connectivity maps between activated areas of the brain. Promising early work in this direction includes photic stimulation BOLD fMRI experiments in humans showing that fMRI measures of visual system activation correlate with measured FA values for the posterior optic pathways, indicating a connection between function (fMRI) and underlying structure (DTI) (10). Fiber tracking has also been used to study the alteration in fiber geometry in pathologic processes. For example, it has been shown that the optic radiations in patients with optic neuritis localize more inferiorly and more laterally than in control subjects (11). Fiber tract mapping also finds application in characterization of white matter tracts that are distorted or destroyed by neoplastic processes, potentially serving as a preoperative, postoperative, and even intra-operative guide to surgical care (Fig. 2) (12).

**Brain Maturation and Aging**

While the precise cause of diffusion anisotropy is not definitively known, results from several groups have shown that diffusion anisotropy in white matter is related in part to the water content of the tissue, the degree of myelination of the tissue, and the extent to which the tissue shows macro-organization (gathering into tightly packed bundles), the latter two factors ostensibly providing barriers to diffusion and allowing preferential diffusion along a given direction (13–20). It is therefore natural to hypothesize that the myelination process can be followed with DTI. It can be shown, for example, that the ADC decreases and the FA increases as human brains myelinate, proceeding from premature to near-term (21), as newborns (19,20,22–26), and into childhood until maturation and young adulthood (27–30). There appears to be a decrease in the FA and...

Ischemia and Wallerian Degeneration

Reduced oxygen delivery to a region of the brain results in cerebral ischemia. As a result of this ischemia, there is movement of sodium and calcium into the cell, osmotic cellular swelling, and a decrease in the fraction of extracellular water (36). These and other changes in the local environment of water molecules can be expected to affect the ADC, and it has long been observed that the ADC is exquisitely sensitive to very early changes in response to ischemia (37-43). However, the precise mechanisms for the observed changes in diffusion during stroke are not yet completely understood.

In white matter, there is a potential to miss early changes related to stroke if diffusion sensitivity is applied along a single direction. This is generally avoided by acquisition strategies that sensitize the images to the trace or average ADC or use isotropic diffusion weighting (44,45). It has been shown that anisotropy indices do not change as quickly in response to hyperacute ischemia as do the various diffusivity indices (46-48). Presumably this phenomenon relates to the lack of disruption of the macrostructure—the myelination and fiber organization—that contributes to the diffusion anisotropy (36). In the acute, subacute, and chronic phases following ischemia, significant anisotropy changes have been observed. For example, in the first 24 hours following the reduction of oxygen delivery, there is an acute rise in anisotropy, possibly due to cellular swelling that leads to tighter packing of axons in a bundle (49). This packing may result in an increased barrier to transverse diffusion in the affected bundles. As the ischemia progresses, the consequent loss of organizing structure results, as expected, in a drop in diffusion anisotropy (50,51). These changes are more marked in white than gray matter, the latter of which does not show marked diffusion anisotropy to begin with. Considerable insight into the pathophysiology of ischemic changes in white matter can be gleaned from diffusion anisotropy experiments. An excellent review of this material has been provided by Sotak (36).

Wallerian degeneration, or degeneration of axons distal to a focus of injury in the brain, can also be seen with DTI, manifesting as a loss of anisotropy in the involved tracts (18,52-57). Although T2-weighted images show signal alterations in the presence of Wallerian degeneration, DTI methods are more sensitive.

Demyelinating Disorders

Due to its inherent sensitivity to disruption of barriers to diffusion such as myelin sheaths and tight cell packing, DTI has the potential to complement existing magnetic resonance techniques in the evaluation of demyelinating disorders such as multiple sclerosis (MS). A number of groups have shown that in comparison to normal-appearing white matter (NAWM), MS lesions show elevated ADC and diminished anisotropy indices such as FA (58-67), with the anisotropy indices being more sensitive for lesion detection than pure ADC measurement (61,63,67). Figure 3 depicts MS lesions imaged at a 3.0 Tesla field strength with disruption of white matter tracts evidenced by FA map abnormalities.

Some studies suggest that the degree of diffusion changes correspond to the severity of the demyelinating lesions, which may prove to be of great clinical importance (58,67). Acute, enhancing lesions also show larger diffusivities and lower FA values than chronic, non-enhancing
lesions. Moreover, DTI shows that NAWM in MS patients has a higher ADC and lower FA than the white matter in normal subjects, suggesting that there is occult damage to white matter in MS that is not seen with other imaging techniques (60,65,67). One preliminary study indicates that there may be a correlation between clinical severity of disease (for example, cognitive impairment in relapsing-remitting MS), and the calculated diffusivities and FA (68).

**Tumor Imaging**

Conventional MRI has long been the mainstay for evaluating central nervous system (CNS) tumor morphology and invasiveness. Diffusion imaging has been shown to be useful in helping characterize neoplasm for tumor necrosis, peritumoral edema, and tumor cellularity (57,69-73). It is unclear if measurement of anisotropy adds additional sensitivity in characterizing CNS tumors. Some authors indicate that there is questionable utility for tumor characterization from DTI imaging and calculation of anisotropy indices (74-77). Other recent reports, however, are more encouraging about the possibility of using DTI to characterize tumor infiltration (78), differentiation of high-grade from low-grade tumors (77), and characterization of peri-tumoral edema (77).

There is little disagreement, however, that DTI will prove to be useful to evaluate distortion of brain white matter tracts within or adjacent to tumor, potentially altering surgical management. The effect of the neoplasm on the white matter tracts can be depicted by plotting the anisotropy indices or more elegantly by diffusion tractography (12,79-81) (Fig. 4).

Enhancing lesions that arise on routine follow-up brain MRI at the site of a previously identified and treated primary intracranial neoplasm present an important diagnostic dilemma. MRI cannot reliably discriminate tumor recurrence or progression from the inflammatory or
necrotic changes resulting from radiation (82). Whereas radiation injury may exhibit telltale morphologic changes, such as a “soap bubble” pattern (83), or a necrosis metabolic pattern as measured by magnetic resonance spectroscopy (84,85), these indicators are not entirely specific. In a recent preliminary study evaluating new contrast-enhancing lesions in patients previously treated for brain neoplasm, (86) substantial differences between recurrent neoplasm and radiation injury could be demonstrated when measuring FA and FA ratios (ratio of FA in the lesion to the FA on the contralateral side). Higher FA values and significantly higher FA ratios were found in NAWM outside the boundaries of peri-lesional edema in patients with radiation injury compared with those with recurrent tumor. One explanation for the difference is that in recurrent tumor, the affected white matter tracts are less well-organized, resulting in a more marked decrease in anisotropy than that observed in tracts affected by radiation damage. This explanation is supported by a previous study where it has been shown that tumor can be distinguished from peri-tumoral vasogenic edema using DTI (77).

**Trauma**

Traumatic brain injury and its effect on the measured diffusion tensor is as yet an understudied topic in radiology. Focal brain injuries such as hematomas and contusions are well characterized by a combination of CT and traditional MRI. Less well-characterized by traditional imaging methods is diffuse axonal injury (DAI), thought to occur in shear injury as a result of abrupt deceleration or abnormal rotation of brain tissue and the subsequent frictional effects of unequally rigid tissues sliding against each other. The effect on white matter tracts is that of stretching of axons and distortion or even disruption of white matter tracts. Case
reports and early studies indicate that DTI holds considerable promise in helping delineate the location and extent of DAI, potentially serving as an adjunct to T2-weighted imaging, which allows sensitive detection of DAI due to the susceptibility artifacts produced by hemoglobin and breakdown products in microhemorrhages (87–91). DTI studies indicate that FA decreases in DAI, reflecting the disruption of underlying tissue organization. The extent of DTI abnormality correlates with clinical markers such as the Glasgow Coma Scale (89,90).

**FUTURE DIRECTIONS**

In the little over ten years since the introduction of the technique, DTI has quickly gone from a technical innovation to an important scientific and clinical tool. Applications of the technique include fiber tracking and determination of connectivity between different areas of the brain, evaluation of white matter maturation, and imaging of ischemia, myelination disorders such as MS, neoplasms, and traumatic brain injuries. Further applications are almost inevitable as research continues to help make the technique more robust and easier to apply, and as more scientists and clinicians gain an understanding of DTI and the information about structure and function that it can provide. Also, further technical innovations in resolution of fiber directions and crossing fibers will also allow the imaging of subtle white matter and fiber tract pathology.

**APPENDIX**

**Diffusion Imaging**

Mathematical descriptions of the macroscopic and microscopic consequences of diffusion phenomena were originally provided by Fick and Einstein, respectively (92,93). Diffusion can be described as the process of transport of matter due to the random motion of molecules in a given medium (94). When the diffusing substance and the medium are the same, the measured coefficients are referred to as self-diffusion coefficients. While MRI provides the ability to study a number of chemicals and nuclei, diffusion MRI is most commonly used to study the self-diffusion of water.

The sensitivity of the nuclear magnetic resonance (NMR) signal to the effects of diffusion has been known since very shortly following the discovery of NMR. This effect has long been used to measure diffusion coefficients (95–97). By the mid-1980s, NMR techniques and analysis had been applied to imaging to obtain pixel-wise ADC maps (98–102). Most modern diffusion imaging techniques rely on variations of bipolar pulsed field gradient methods (97) to obtain diffusion sensitivity. In these sequences, two magnetic field gradients are applied sequentially to de-phase and then re-phase spins or protons. Any spins that have moved in the interval between the two gradients do not “feel” the same magnetic field as during the first gradient, and thus they do not get re-phased, resulting in a net loss of spin coherence. This results in a quantifiable loss in the MRI signal, which can be related to the ADC. In the simplest case, with spin-echo MRI and considering for the moment only a single diffusion coefficient per voxel, it can be shown that the signal and the ADC are related as follows:

\[ S = S_0 e^{-b D} \]

where \( S \) is the measured signal, \( S_0 \) the signal in absence of the gradients, and \( D \) is the ADC. The \( b \) or so-called b-factor in this equation is a function of the gradient strength \( G \), duration \( \delta \), and time separation \( \Delta \) between the gradient pulses. The b-factor must be calculated for each sequence, which can be non-trivial when the diffusion gradients interact with the imaging gradients in a complicated fashion. For the simple case where imaging gradients and the resultant cross terms in the b-factor calculations are ignored,\[ b = \gamma G^2 \delta^2 / (D \cdot \delta/3), \]

where \( \gamma \) is a physical constant, the gyromagnetic ratio. \( D \) can be determined from Equation 1 if at least two images are acquired with different diffusion weightings (and thus different b-factors). It also becomes evident from this equation that any movement of spins during the diffusion time \( \Delta \) will result in MRI signal loss. Thus diffusion MRI is sensitive to all motion of molecules during the sequence, and not just purely diffusive motion. Moreover, the observed diffusion coefficients in tissues reflect diffusion in several compartments (extracellular and intracellular, intranuclear, mitochondrial, etc.) which may all have different diffusivities if one could resolve them. It is for these reasons that the diffusion coefficient and tensor as measured with MRI are called the apparent diffusion coefficient (ADC) and apparent diffusion tensor (ADT), respectively.

**The Diffusion Tensor**

In an environment where the barriers to diffusion are identical in all directions, diffusion is considered isotropic. This is the case, for example, in a cup of water, where even if molecules are allowed to diffuse for relatively long times, they are unlikely to encounter a barrier to diffusion such that movement in one direction would be favored over any other. In such situations, the diffusion coefficients in all directions are the same, hence the term isotropic diffusion. For isotropic cases, measurement of a single scalar coefficient suffices to completely characterize the system. However, the diffusivity of a substance cannot always be assumed identical in all directions. Diffusion coefficients can be relatively large in one direction, and small in
another. For medical applications, this is the case for example in white matter, muscle, cartilage, and in the lens of the eye (103–109). In such settings, diffusion is said to be anisotropic, reflecting the non-equal diffusivities in various directions. Diffusion is more generally characterized by a second order tensor, or a matrix of nine coefficients:

\[
D = \begin{bmatrix}
D_{xx} & D_{xy} & D_{xz} \\
D_{xy} & D_{yy} & D_{yz} \\
D_{xz} & D_{yz} & D_{zz}
\end{bmatrix}
\]  

\[\text{[2a]}\]

This implies that nine diffusivities would have to be determined to measure the tensor. However, the diffusion tensor is symmetric, meaning that \(D_{xy} = D_{yx}, D_{xz} = D_{zx}, \) and \(D_{yz} = D_{zy}.\) Thus, only six diffusivities need to be determined. When the axes of the measurement system coincide exactly with the axes of the fiber or object being studied, the off-diagonal elements of the tensor (i.e., \(D_{xy}, D_{xz}, \) and \(D_{yz}\)) become zero, and the measured diagonal diffusivities \(D_{xx}, D_{yy}, \) and \(D_{zz}\) are termed the principal diffusivities, often annotated \(D_{11}, D_{22}, \) and \(D_{33}\) or \(\lambda_1, \lambda_2,\) and \(\lambda_3,\) as given by Eq \([2b]:\]

\[
D_{\text{prin}} = \begin{bmatrix}
\lambda_1 & 0 & 0 \\
0 & \lambda_2 & 0 \\
0 & 0 & \lambda_3
\end{bmatrix}
\]  

\[\text{[2b]}\]

Of course, in the general case, the measurement and principal axes of diffusion do not coincide for most fibers. In such a case, these principal diffusivities which are also called the eigenvalues of the diffusion tensor, along with the eigenvectors of the system (defining the directions of the principal diffusivities), can be calculated from the measured tensor by a simple mathematical transformation relating the measured tensor (Equation \([2a]\)) to the principal diffusivities (Equation \([2b]\)).

Basser et al (1,110) provided the seminal work depicting the measurement of the ADT with MRI. Starting with the mathematical expressions for the description of magnetization in the presence of spin diffusion (96), they derived the expressions necessary to calculate the various terms of \(D\) (or ADT) from an MRI experiment. They showed that

\[
S = S_0 e^{-\frac{1}{3} \sum_i \sum_j b_i D_{ij}}
\]

\[\text{[3]}\]

where

\[
b_i = -\gamma \int G_i \, dt \int G_j \, dt \, dt
\]

\[\text{[4]}\]

Here, the indices \(i\) and \(j\) represent the measurement axes (1, 2, and 3 being \(x, y,\) and \(z,\) respectively), \(G_i\) and \(G_j\) thus represent the applied diffusion gradients in various directions. Equation 3 bears obvious resemblance to Equation 1, the case for measuring a single diffusion coefficient. However, all six unique diffusivities must be accounted for, and thus Equation 3 implies that at least seven images must be acquired to completely determine the seven variables in this equation \((S_0\) and the six unique diffusivities). Obviously, the calculation of the b-matrix as per Equation 3 is considerably more complex than that of b-factors for a unidirectional experiment, and care must be taken to account for the interaction between the various diffusion and imaging gradients.

Data interpretation in DTI can be difficult. The information contained in the six diffusivities of the measured tensor or in the eigenvalues and eigenvectors of the system has to be displayed, and the information contained within the datasets further extracted. DTI reveals much architectural information about the various fiber tracts being studied. Scalar invariants are calculated from the measured diffusivities obtained from a DTI experiment and are not dependant on gradient directions and their relationship to the subject. Several such invariants, which are easy to conceptualize and display, have been used in DTI. These quantities are useful in that they provide structural information about the diffusion system, and along with the eigenvalues and eigenvectors of the system, are independent of the measurement axes across data sets. The diffusion trace \((\text{Tr}(D))\) is calculated as follows:

\[
\text{Tr}(D) = \lambda_1 + \lambda_2 + \lambda_3
\]

\[\text{[5]}\]

The trace, or mean diffusivity \((\lambda) = \text{Tr}(D)/3)\) gives information about the overall mobility of water molecules in the environment being studied. Several scalar invariants have been suggested to give information about diffusion anisotropy. The most commonly used of these quantities are FA and relative anisotropy (RA), which are calculated as follows:

\[
\text{FA} = \sqrt{\frac{3}{2}(\lambda_1 - \langle \lambda \rangle)^2 + (\lambda_2 - \langle \lambda \rangle)^2 + (\lambda_3 - \langle \lambda \rangle)^2}
\]

\[\text{[6]}\]

\[
\text{RA} = \frac{(\lambda_1 - \langle \lambda \rangle)^2 + (\lambda_2 - \langle \lambda \rangle)^2 + (\lambda_3 - \langle \lambda \rangle)^2}{3 \langle \lambda \rangle}
\]

\[\text{[7]}\]

FA and RA are similar in that both quantify the degree of diffusion anisotropy in the tensor. FA ranges from 0 (completely isotropic) to 1 (completely anisotropic diffusion), while RA ranges from 0 to \(1/2.\) FA and RA maps are often depicted for DTI data, as they, along with the \(\langle \lambda \rangle,\) offer computationally and conceptually the simplest yet quantitative insight into diffusion anisotropy in the system. Another frequently encountered measure of anisotropy, \(A_n,\) is not shown here but is closely related to RA.

As a rough guide to the reader, we provide parameters used for a typical clinical ADT experiment and the
quantitative information that is often extracted from it. A routine ADT examination at our institution consists of collecting single-shot echoplanar imaging (EPI) with diffusion weighting in 10 directions (including b = 0), a field of view of 32 cm encoded with a 160 × 120 matrix, and 2 signal averages. Since the EPI images are collected as single shots, the imaging time is small (~five minutes including sequence setup time), though the images must be post-processed to obtain the diffusivity and anisotropy information. This latter process also usually requires a few minutes, though it can be more time consuming, especially if quantitative data about given lesions are to be obtained and analyzed. The average diffusivity in the brain tends to range around 0.7 mm²/s, while the FA in the highly organized adult corpus callosum, which shows marked diffusion anisotropy, is approximately 0.75 mm. Cerebrospinal fluid in the ventricles, which shows essentially isotropic diffusion, yields FA values of 0–0.15. However, these are values used for typical clinical experiments and acquisition and processing times can be considerably longer for more complicated DTI techniques such as High Angular Resolution Diffusion Imaging, in which diffusion is encoded in a very large number of diffusion directions (111,112).

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Cerebral Venous Pressure, Intra-Abdominal Pressure, and Dural Venous Sinus Stenting in Idiopathic Intracranial Hypertension

Deborah I. Friedman, MD

Abstract: Increased pressure in the dural venous sinuses has been proposed as the cause of increased intracranial pressure in the condition known as idiopathic intracranial hypertension (IIH). This hypothesis has received further support from manometry of the dural venous sinuses, showing a substantial proximal-to-distal pressure gradient, and from reports of improvement of IIH following stenting of the dural sinuses. Increased intracranial venous pressure has also been proposed as the cause of IIH in morbid obesity through increased abdominal pressure that is transmitted through the thorax to the cerebral draining veins. Although these hypotheses are intriguing, neither has enough scientific support to be endorsed yet. Moreover, dural venous sinus stenting should not be adopted as a therapeutic procedure in IIH until larger clinical trials attest to its safety and efficacy.

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VENOUS HYPERTENSION AND INCREASED INTRACRANIAL PRESSURE

Although the mechanism of idiopathic intracranial hypertension (IIH) is uncertain, the cerebral venous system has been implicated since the 1930s. Dandy (1) hypothesized that the volume of cerebrospinal fluid (CSF) or cerebral blood might be increased. Others postulated that the cerebral microvasculature was the source of cerebral edema in this condition (2-4). Intracranial venous hypertension has been proposed as a unifying mechanism or final common pathway of IIH. Johnston et al (5) first suggested that increased sagittal sinus pressure causing decreased CSF absorption was the underlying cause. A clinically identical syndrome to IIH is produced by cerebral venous sinus thrombosis (6-8).

The interest in the concept that the dural venous sinuses were the source of increased intracranial pressure in IIH was heightened in the 1990s with studies of direct venous manometry in IIH patients and studies performed in IIH patients undergoing bariatric surgery. Intracranial and central systemic venography and manometry were performed in ten patients (three men, seven women, aged 2-40 years) with increased intracranial pressure from various causes (one congenital stenosis, two idiopathic, five morbid obesity, one tumor compressing the dural sinus, one cranio-diaphyseal dysplasia and bony overgrowth of the skull) (9). All patients had CSF pressure over 200 mm water and no ventriculomegaly. No venous outflow obstruction was found in the obese patients but some degree of stenosis or occlusion was seen in the other five patients (including those with congenital stenosis and tumor). Superior sagittal sinus pressure was elevated in all seven patients in whom it was measured, including the five obese patients. The mean increase was small (1.8 mm Hg above normal) in patients without obstruction, and it is uncertain whether the elevation was statistically or clinically significant. Central venous pressure was measured in six of the seven patients who had venous sinus manometry and was abnormal in five. Patients with venous sinus occlusion were treated with angioplasty/thrombolysis or shunting. The patient with the tumor underwent a CSF diversion procedure (shunt), and the patients with IIH were treated with a combination of shunt, optic nerve sheath fenestration, or gastric stapling. None of the measurements was repeated following treatment.

INCREASED VENOUS PRESSURE AND INCREASED INTRACRANIAL PRESSURE IN MORBID OBESITY

The concept that cerebral venous pressure plays a causative role in IIH has led to the theory that increased...
abdominal pressure in obesity results in impaired venous return to the heart and that this results in increased intra-cerebral venous pressure. Patients with morbid obesity were studied to determine the relationship between sagittal abdominal diameter (central obesity) and intra-abdominal pressure (10). Eighty-four consecutive patients (67 women, 17 men) undergoing surgery for morbid obesity and five non-obese patients having other abdominal procedures were studied. Measurements were obtained on patients lying in the supine position on the operating table. Intrabdominal pressure was estimated from urinary bladder pressure via bladder catheterization and manometry at end-expiration, and sagittal abdominal diameter was measured from the table to the apex of the abdomen. Urinary bladder pressure was highly correlated to abdominal diameter but not with waist circumference.

The same investigators measured intrabdominal pressure and cardiac filling pressures in obese patients with IIH, five at the time of gastric bypass surgery and one undergoing laparoscopic adjustable gastric banding (11). Bladder pressure, pulmonary artery wedge pressure, and pleural (transesophageal midthoracic) pressures were determined. Urinary bladder pressure was significantly higher in all six subjects with IIH than in the five non-obese patients reported in the previous study (10). Statistical analysis was not provided to determine whether the values in the patients with IIH significantly differed from those of the obese control subjects studied previously, allowing for differences in baseline weight. Pleural pressure was only obtained in three subjects and wedge pressure was not obtained in the prior study for comparison.

Eight morbidly obese women aged 26–43 with IIH were studied over an 11-year period after undergoing gastric weight reduction surgery (11). It is uncertain whether the study was prospective or whether the patients were accrued consecutively and inclusively. All had CSF pressures above 250 mm of water prior to surgery; all had received other treatments and three had resolution of their papilledema with persistent headaches. Obstructive sleep apnea and obesity hypoventilation syndrome were noted in two patients each. Seven patients had undergone a proximal Roux-en-Y bypass procedure and one had undergone a distal gastric bypass procedure. All patients experienced significant weight loss, averaging 57 ± 5 kg at 34 ± 8 months postoperatively. Papilledema, sleep apnea, and obesity hypoventilation syndrome resolved in all. Headache resolved or improved in all patients. The authors concluded that significant weight loss was an effective treatment for IIH in morbidly obese individuals. They postulated that curing the obesity-related hypercapnea may have been a factor. They also proposed, apropos the previous study, that central obesity caused "increased intrabdominal pressure, elevating the diaphragm and leading to increased pleural pressure that would then decrease venous return from the brain to the heart. This hypothesis is consistent with the theory that IIH is secondary to increased cerebral venous pressure" (11).

The premise that central obesity produces increases intra-abdominal pressure with the pressure vector directed inward is not supported by physics or physiology. It does not account for the effect of gravity in the upright position or the distensibility of the skin and soft tissue enclosing the abdomen. This theory also fails to explain the fact that the incidence of IIH does not change during pregnancy, where the enlarging fetus compresses the inferior vena cava, producing venous hypertension (12). Additionally, although the incidence of IIH has doubled since the late 1980s, coincident with the increased prevalence of obesity in the United States, one would expect a more dramatic rise in IIH cases given the premise of this theory (13). In summary, while IIH was associated with elevated systemic venous pressure, there is currently no evidence that obesity is the cause of increased intracranial pressure (ICP).

**DURAL VEINOS SINUS STENOSIS IN IDIOPATHIC INTRACRANIAL HYPERTENSION**

A vexing question is whether dural venous sinus stenosis causes IIH. Magnetic resonance venography (MRV) and conventional angiography with venous imaging are often normal when a substantial pressure gradient is present. But auto-triggered elliptic-centric-ordered three-dimensional gadolinium-enhanced (ATECO) MRV demonstrated transverse dural sinus stenosis in 90% of 29 IIH patients (14) with a high inter-rater correlation.

King et al (15) studied nine patients with IIH and two patients with minocycline-induced intracranial hypertension by CT, MRI, digital subtraction internal carotid arteriography, and dural sinus venous manometry (15). Venous pressure was measured in the superior sagittal, left sigmoid, and transverse sinuses. Pullback pressures were measured in the superior sagittal sinus, torcular Herophili, proximal and distal transverse sinuses, sigmoid sinuses, and jugular bulbs. Normal controls were not used because the procedures are invasive. All nine IIH patients had increased pressure in the superior sagittal sinus (14–23 mm Hg; normal = 2–7 mm Hg) and proximal transverse sinus. There was a large (10–20 mm Hg) pressure gradient between the superior sagittal sinus and the internal jugular vein in IIH patients. The angiography findings did not always correlate with the manometry findings. A gradually tapered narrowing of the transverse sinus was frequently observed. The authors proposed that a mural thrombosis associated with thrombotic factors related to obesity was the cause of the dural sinus stenosis and pressure gradient. The patients
with minocycline-induced intracranial hypertension had normal studies.

The same researchers subsequently performed an elegant study confirming the reciprocal relationship between cerebral venous pressure and CSF pressure (16). Twenty-one patients with confirmed IIH underwent digital subtraction internal and external carotid angiography, dural sinus venography, and manometry. Immediately afterward, eight of these patients underwent lateral C1-2 puncture and their CSF pressure was recorded before and after 20–25 mL of CSF was removed, after which the cerebral venous pressure measurement was repeated. Control subjects consisted of patients with other diagnoses or those who were suspected of having IIH, but the diagnosis was later proven incorrect. Nineteen of the 21 IIH patients showed a large pressure gradient across the transverse venous sinus. Lowering of the ICP by removal of CSF produced a pressure drop within the transverse sinus between 12–41 mm Hg in six patients. The pressure drop in the other two patients was 4 mm Hg and 6 mm Hg, respectively; both patients had only a small drop in CSF pressure after the cervical puncture. The drop in pressure in the proximal transverse sinus was most dramatic in patients with the highest pressures before the cervical puncture. Their results correlate nicely with the previous studies showing that at high ICPs, the transverse sinuses could collapse, producing increased superior sagittal sinus pressure (17,18). Based on this work, most investigators have concluded that increased venous pressure results from, rather than causes, increased ICP in IIH (19).

**CONCLUSIONS**

Venous sinus thrombosis with secondary venous hypertension is a well-recognized cause of intracranial hypertension. However, the relationship of venous sinus stenosis to IIH is less well defined. Most reports suggest that venous sinus stenosis and venous hypertension are likely the manifestations of increased ICP rather than the cause of it.

The relationship between the cerebral venous system and intracranial pressure in the pathogenesis of IIH is intriguing. However, there is presently insufficient evidence to endorse the theories of systemic or central venous hypertension as the underlying cause. Even if dural venous blockage is a cause or the only cause of IIH, larger clinical studies of stenting must demonstrate the long-term safety and efficacy of this procedure before it can be adopted for IIH cases refractory to standard treatment methods. Because standard medical treatment is generally successful
and much less invasive, stenting should not be adopted until such measures have failed.

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Abstract: Based on the favorable clinical results in acute spinal cord injury, high-dose methylprednisolone at an intravenous loading dose of 30 mg/kg followed by a continuous infusion of 5.4 mg/kg/h for 24 or 48 hours has been adopted for the treatment of acute traumatic optic neuropathy (TON). Although there is anecdotal evidence of the efficacy of high-dose corticosteroid in this condition, there are no prospective, randomized trials to attest to its benefit. On the other hand, the largest retrospective study showed no benefit of high-dose corticosteroid treatment of TON. Moreover, subsequent study of such treatment of acute spinal cord injury has disclosed that the clinical benefit is modest and that treatment is actually harmful if administered more than eight hours after injury. A recently reported placebo-controlled randomized clinical trial of high-dose corticosteroids in head injury was stopped prematurely because of a significantly greater mortality in the corticosteroid-treated patients. Recent experimental studies suggest that methylprednisolone may be harmful to the optic nerve. Considering this clinical and experimental evidence, there is no basis for treating TON with high-dose corticosteroid.

WHAT IS HIGH-DOSE CORTICOSTEROID AND WHY HAS IT BEEN USED FOR TRAUMATIC OPTIC NEUROPATHY?

High-dose corticosteroid refers to an intravenous loading dose of methylprednisolone at 30 mg/kg followed by a continuous infusion of 5.4 mg/kg/h for 24 or 48 hours. This protocol was used to treat spinal cord injury in the second and third National Acute Spinal Cord Injury Studies (NASCIS II and NASCIS III) (3,4). It was widely adopted for treatment of TON after the NASCIS II reported in 1990 that patients with spinal cord injury, if started on this protocol within eight hours of injury, had a better clinical outcome than placebo-treated patients (5).

The scientific rationale for the use of this protocol was based on research into the mechanisms of action of corticosteroids conducted by Demopoulos (6), Flamm (7), and Seligman (8) at New York University; Hall and Braughler (9) at the Upjohn Company; and Anderson et al (10) at the University of Cincinnati. Their work led to the hypothesis that pathologic free radical reactions are initiated following major central nervous system trauma and that very high doses of corticosteroid functioned as antioxidants to inhibit free radical damage. Doses of methylprednisolone in the 15-30 mg/kg range were found to improve microcirculation, energy metabolism, post-injury histology, and functional outcomes in animal models of spinal cord injury (7,11,12).

The NASCIS II was a multi-center, randomized, double-masked, and placebo-controlled study of acute spinal cord injury (3). Patients were randomized to one of three treatment arms within 12 hours of injury: placebo, naloxone, or methylprednisolone. Patients treated with high-dose methylprednisolone within eight hours of injury had a small but measurable improvement in motor and sensory function compared with placebo-treated patients. But those treated with either medication more than eight hours after injury did not demonstrate an improvement in neurologic scores.
compared with placebo-treated patients. In fact, a post-hoc analysis of this study found that methylprednisolone treatment started more than eight hours after injury was actually detrimental to outcome (13).

STUDIES OF TREATMENT OF TRAUMATIC OPTIC NEUROPATHY
Since 1990, 16 major studies have reported the treatment of 715 patients with TON. 500 of whom received corticosteroid. None of these studies had appropriate controls and many had other substantial design flaws (5). Even the International Optic Nerve Trauma Study was a non-randomized, uncontrolled study with a lack of uniformity regarding corticosteroid dose, timing of treatment, and indications for optic canal decompression (2). A casual examination suggests that treated patients in recent studies have better visual outcomes than do untreated patients from older studies. However, recent treatment studies tend to identify optic nerve trauma patients closer in time to the initial injury, making improvement more likely irrespective of whether they are treated (5).

EXPERIMENTAL STUDIES
Since the International Optic Nerve Trauma Study, three studies have been published examining the effects of high-dose methylprednisolone on experimental optic nerve injury and one on its effects on experimental optic neuritis. Two experimental TON studies (14–16) involved ten-second optic nerve crush injuries that produced nearly complete disruption of all optic nerve axons. In the first study, by Ohlsson et al (14,15), high-dose methylprednisolone had no discernible effects, which is consistent with such a severe injury.

In the second experimental TON study, Sheng et al (16) were able to show that high-dose methylprednisolone reduced the number of retinal ganglion cells that showed evidence of apoptosis. This effect may become clinically important if techniques are developed to regenerate injured optic nerves, in which case methods of preserving retinal ganglion cells will be critical.

My experimental TON study (17) involved a five-second optic nerve crush injury in rodents that leaves intact approximately 25% of optic nerve axons. Thirty minutes after injury, animals received one of five intravenous treatments: saline, methylprednisolone 30 mg/kg, 60 mg/kg, 90 mg/kg, or 120 mg/kg, repeated at six-hour intervals for three additional treatments. Following a six-week recovery, the remaining axons in the injured nerves were counted. Saline-treated animals retained the greatest number of axons and there was a dose-dependent decline in axons with increasing doses of methylprednisolone. Methylprednisolone exacerbated axonal loss ($P < 0.02$) (17). The study left unexplored whether a lower dose of methylprednisolone would be helpful.

Diem et al (18) examined the effect of high-dose methylprednisolone on experimental autoimmune optic neuritis. In their study, methylprednisolone significantly increased apoptotic retinal ganglion cell loss. Methylprednisolone in a dose of 20 mg/kg was administered once the animal developed optic neuritis to simulate pulse treatment. It was found that, compared with controls, animals with optic neuritis treated with methylprednisolone possessed fewer surviving retinal ganglion cells. This decline corresponded to functional visual deterioration based on visual evoked potential testing.

CONCERNS ABOUT CORTICOSTEROID TREATMENT OF ACUTE SPINAL CORD INJURY
Several investigators have raised questions regarding the perceived efficacy of methylprednisolone for acute spinal cord injury and its inherent safety (19–21). NASCIS II appeared to be a vindication of 30 years of basic science research on spinal cord injury that had suggested that methylprednisolone was neuroprotective. However, clinical improvement was modest. This limited benefit has to be weighed against the increased risk of sepsis and pneumonia found among patients treated with corticosteroids for 48 hours in the NASCIS III (4). Some critics have suggested that without stratifying patients between those treated within eight hours and after eight hours of spinal cord injury, the NASCIS II would not have shown a beneficial effect for methylprednisolone (19). These critics suggest that the time frame of eight hours was based on post-hoc analysis rather than a planned analysis point. The distinction is important because post-hoc stratification permits bias in the presentation of data. Defenders of the study answer that a time stratification of the data was always intended (22).

THE CORTICOSTEROID RANDOMIZATION AFTER SIGNIFICANT HEAD INJURY TRIAL RESULTS
The results of the Corticosteroid Randomization After Significant Head Injury (CRASH) trial (23) raise further concerns about corticosteroid treatment of head trauma. CRASH was a multi-center, randomized, and placebo-controlled study that investigated the value of methylprednisolone in the treatment of head trauma. Patients were randomized within eight hours of injury to placebo or high-dose methylprednisolone for 48 hours. The goal of recruiting 20,000 patients into the study was never reached because the study was stopped at 10,005 patients when safety monitoring data revealed a higher risk of death from all causes at two weeks after trauma in the methylprednisolone-treated.
patients (21%) than in the placebo-treated patients (18%, \( P = 0.0001 \)). The CRASH study results are relevant because TON is associated with loss of consciousness in 40%–72% of cases (5).

These clinical findings, together with the newer experimental data, provide a very cogent rationale for withholding high-dose methylprednisolone in TON.

REFERENCES


Scope: This 500-page book covers the fundamental topics in neuro-ophthalmology in 50 chapters written by respected specialists. Its aim is to provide very practical guidance to ophthalmologists and neurologists. There are relatively few references. Some chapters have no references, providing only suggested readings. As such, this is more of a manual than a textbook. It is divided into four sections: examining techniques, principal manifestations, principal conditions, and procedures.

Strengths: The field is broadly covered and the critical information is highlighted with flow-charts, tables, bulleted text, and illustrations. Many of the chapters really do tell you how to do things. There is even a chapter on billing for neuro-ophthalmologic diseases.

Weaknesses: The style of presentation and writing quality varies too widely between chapters. Some are elegantly written and nicely organized with an aesthetic appearance. Others consist mostly of bulleted, flagged, or boxed text crowded out by flow charts, schematic illustrations, and patient photographs. The effect is dizzying.

Recommended audience: Ophthalmologists and neurologists.

Critical appraisal: This book contains much practical information, but it is going to have trouble finding an audience. There is too much for the intended audience and too little for neuro-ophthalmologists. The next edition will benefit from greater attention to uniformity of presentation and more judicious use of educational devices.

Jonathan D. Trobe, MD
Kellogg Eye Center
Ann Arbor, Michigan

Manual of Neurologic Therapeutics, 7th Edition


Scope: This is a compact text laid out in 17 chapters that pertain to specific categories of neurological disease. Each chapter then discusses each subcategory of disease using the following headings: background, pathophysiology, prognosis, diagnosis, and treatment. Twenty-eight pages are dedicated to neuro-ophthalmology written by Don Bienfang, MD, but there are other chapters that also discuss various aspects that touch on neuro-ophthalmology.

Strengths: The greatest strength of this book is its compact size. The writing is brief and very economical. The book is pocket-sized and fits well into a white coat pocket for residents and medical students and compact enough for a busy attending's bookshelf. Where this book excels is the clear and concise list of therapeutics for each disease listed. The textbook is also offered on PDA, adding to its viability as a resource.

Weaknesses: To learn more specifics about the clinical presentation of illness, one must look elsewhere. However, more detail would have greatly added to the book's size and portability. Frankly, the section on multiple sclerosis is almost too verbose.

Recommended audience: Neurologists of all experience levels would benefit from this book. It should also be a great book for ophthalmologists who manage neurologic patients with vision problems.

Critical appraisal: This is an excellent small textbook that can be used as a quick reference guide in treating a wide variety of neurologic and neuro-ophthalmologic disorders. This book will assist the reader in determining the basics of a treatment paradigm for many illnesses within a short time of locating the pages in the book.

Robert A. Egan, MD
Casey Eye Institute
Portland, Oregon

Vision: From Neurons to Cognition


Scope: This book is the product of a symposium of the same name held in May 2000 in Montreal. The range of topics is large, ranging from the first chapter on the effects of glutamate in retinal ganglion cells to selective attention. Most of the book is devoted to work based on animal neurophysiology with a de-emphasis of psychophysics, psychology, and neuropsychology.
As with all multi-authored books, there is significant variation among the chapters. There are experimental papers that would be at home in the pages of The Journal of Neuroscience, scientific reviews that advance a particular hypothesis, and basic reviews appropriate for a general audience. This veritable potpourri forces the reader to shift gears in moving between chapters, perhaps not a bad thing. One discovers that this is a collection of papers without a theme, except that all involve vision.

**Strengths:** The chapter by Cowey and Walsh on transcranial magnetic stimulation is as good an introduction to the technique for the uninitiated as I have seen anywhere. The article by Pascual-Leone and Hamilton details an intriguing exploration of the question of what exactly it means for visual cortex to be "visual," by using transcranial magnetic stimulation and functional MRI (fMRI) to study the shift in function of the occipital cortex towards tactile processing in the blind and the blindfolded. Two chapters detail important challenges to the alternate pathway explanations of blindsight. Fendrich, Wessinger, and Gazaniga review their data on the relation of blindsight to islands of surviving vision, and presumably surviving striate cortex; Faubert and Dacconi describe with mathematical detail the potential for intra-ocular scatter to explain the data supporting blindsight in hemidecorticated patients.

This work provides some comfort to Campion, Latto, and Smith who were castigated by the research community for similar arguments in 1982. Schiller and Tehovnik provide a good summary of neurophysiologic data on the role of different cortical regions in generating saccades, complementing the reviews based on human lesions that Pierrot-Deseilligny has written in other periodicals. I found the chapter by Caes and Lyon on whether primates have an area V3 to be an intriguing example of the vagaries involved in defining a cortical area. Last, Goodale provides another excellent overview of the experiments supporting the notion that extrastriate cortex is divided into a dorsal stream for action preparation and a ventral stream for object recognition.

**Weaknesses:** The range of material covered is uneven. At least five of the chapters are devoted to blindsight, the main research field of one of the editors. On the other hand, there is no treatment of face recognition, and there is only one chapter devoted to reading research and the magnocellular theory of dyslexia. Given the explosion in functional neuroimaging, there is a surprising lack of fMRI data. The one chapter on fMRI and the Stroop task has the odd distinction of being the only functional neuroimaging paper I have seen without any figures.

**Recommended audience:** Pure clinicians will not likely consider this book helpful, and those lacking experience in neurophysiology will find the early chapters heavy reading. However, those who are involved in research on cortical visual dysfunction will find much of interest.

**Critical appraisal:** This book should not be sought as a comprehensive review of visual neuroscience. But it is an interesting "Year 2000" snapshot of the state of vision research, particularly in neurophysiology. It is disappointing that the publishers have taken such a long time to deliver such a time-sensitive book. I would have been happier to have it on my shelf a few years ago.

**Active Vision: The Psychology of Looking and Seeing**


**Scope:** In this text, the authors put forward their thesis that the study of vision, in concentrating on phototransduction and signal processing, has ignored the central role of eye movements. They provide a review of their own work and of the scientific literature.

The book contains three sections (nine chapters) that are written by the two authors and their colleagues. The first section (of three chapters) provides background and rationale for the idea of active vision, which the authors contrast with passive vision (the more prevalent view of the visuomotor system). The basic physiology of the retinal pathways and the oculomotor apparatus are reviewed briefly in this context.

The authors define passive vision as being, in part, the notion that an observer can give all points on the classic retinotopic map the same level of attention; the practical matter of foveation suggests otherwise. In the passive vision model, covert attention to extrafoveal targets is postulated to result from the activity of an attentional spotlight. Such a model relies on the notion of a "picture in the head" of the entire environment, a concept the authors believe has erroneously arisen from inappropriate application of earlier research into aural processing. The active vision argument is that eye movements are not randomly generated nor do they result from objects in the visual field being assigned covert visual attention. Rather, eye movements are presented as primary events to facilitate vision by bringing objects of interest onto the fovea, and the typical three to four saccades per second are not merely the consequence of attentional redirection.

The second section (of three chapters) details the pathways by which visual attention is generated and the
The influence of attention on subsequent saccades. Experimental models are detailed, and saccadic latency, intersaccadic pauses, and saccadic redirection are addressed in the context of active vision pathways. Visual scanning is shown to occur in typical patterns which can be altered by presentation of temporally-constrained visual cues. Of particular note is the discussion of visual sampling during reading (chapter five), in which the authors review a significant body of data describing text scanning methods and the effect of distracting words or letters and other unexpected objects.

The third section (three chapters) examines the role of active vision in object-related actions, or tasks in which gaze and attention must be frequently redirected. The integration of eye movements into cognitive processes is explored, and a deictic model of vision is introduced. Eye pointing is predicted to precede physical pointing with a limb or tool to complete the intended task. Such a just-in-time visual representation, where the eyes move to the target of regard just prior to physical movement, is postulated to minimize the brain's computational load (which, in the passive vision model, would be tremendous to maintain a detailed representation of all objects in the environment). The section concludes with an integrated model of saccadic generation and trans-saccadic integration.

Strengths: Very well-written and extensively researched, this text is also concise enough to provide an introduction to the cognitive vision field without being overwhelming. Illustrations are used effectively to explain concepts presented in the text.

Weaknesses: The chapter on human neuropsychology is too brief. While the authors describe a number of interesting syndromes and cases, this chapter seems to raise more questions than it answers.

Recommended audience: While the intended audience includes neuropsychologists, psychology students, and vision researchers, the text is quite accessible to ophthalmologists, neurologists, and others with a core knowledge of the oculomotor system and the neural pathways of visual processing.

Critical appraisal: The authors concisely and convincingly review their own work and that of others to demonstrate that eye movements are an important element in the cognitive process of active vision. They show that a passive model of vision is not sufficient to explain experimental data, and their very readable view of this challenging field of research is to be appreciated.

Prem S. Subramanian, MD, PhD
The Uniformed Services University of the Health Sciences
Bethesda, Maryland

The Cat Primary Visual Cortex

Bertram R. Payne, PhD, and Alan Peters, PhD, Editors.

Scope: This is a comprehensive scientific reference book that encompasses the functional architecture, physiology, and pharmacology of the cat's primary visual cortex.

The cat's visual cortex is the primary model for the study of visual processing, cerebral circuitry, and cerebral processing. The first chapter describes how both areas 17 and 18 process primary signals from the lateral geniculate nucleus in parallel and in distinct and overlapping ways. Subsequent chapters describe the representational architecture of areas 17 and 18 as revealed by optic imaging, 2-deoxyglucose, and functional MRI techniques. These chapters provide an overall view of the functional columnar architecture of cat primary visual cortex at the level of neural systems. The anatomic studies depict the organization of afferent and efferent connections within one hemisphere and between hemispheres. Next, long-range intrinsic circuitry is reviewed from the perspective of anatomy and the emergence of orientational and directional preferences of neurons. The ending chapters provide a review of the relationship between B- retinal ganglion cells and the primary visual cortex, the role of the primary visual cortex in visually-guided behavior, high acuity vision, hyperacuity, and stereoscopic depth perception.

Strengths: This book gives the relevant details necessary for understanding the scientific basis of visual processing. The references listed at the end of each chapter are an excellent resource for most of the classic literature.

Weaknesses: None.

Recommended audience: This is an excellent reference book for the neuroscientist and the neuro-ophthalmologist involved in basic research on the primary visual cortex.

Critical appraisal: This book summarizes the continuing saga of the exciting research pioneered by Nobel Prize winners David Hubel, PhD and Torsten Wiesel, PhD. It is one of the best books to read for a better understanding of the cortical processing of visual signals.

Jane W. Chan, MD
University of Nevada School of Medicine
Las Vegas, Nevada
Book Reviews

The Neuropsychology of Vision


**Scope:** This book takes on the daunting task of evaluating the wealth of information that has been collected over the past few decades concerning visual perception and cognition. Bringing together the knowledge of 17 vision researchers from Europe and the United States, the book expertly and easily clarifies the numerous studies that have been performed on both animals and humans that define what we presently know about the process of vision. It is well-written and leads the reader, in an understandable way, from the retinal ganglion cell to the rehabilitation of patients with cerebral visual disorders.

The book is a collection of 11 chapters written by leading vision researchers, each discussing their particular area of expertise. The chapters are logically grouped into six parts that begin with the anatomy and physiology of the visual system and lead to the increasingly complex concepts of psychophysical studies and recovery of cognitive function. The illustrations adequately compliment the text to help explain visual pathways and research models. Also included are several color plates to help with the understanding of chromaticity and luminance. There is an excellent and extensive bibliography at the end of each chapter to allow for a deeper understanding of each subject.

**Strengths:** This is an excellent review of the present state of research on the intricate workings of visual perception, processing, and cognition. The text is surprisingly straightforward and easy to read, especially for anyone with a basic understanding of the anatomy and physiology of the visual system. The book describes in great detail what we presently understand about visual perception and the clinical syndromes associated with cerebral lesions that affect visual consciousness. The chapters on color perception and motion detection help untangle the confusing plethora of pathways.

**Weaknesses:** There are few weaknesses in this text, especially when one considers the amount of research that has been generated about visual processing since the seminal work of Hubel and Weisel over four decades ago. The last two chapters on “Perception, Memory, and Agnosias” and “Recovery and Rehabilitation of Cerebral Visual Disorders” are relatively sparse; they could have included more case studies and research relevant to the clinician. Some of the information has already been modified by studies published in the year since this book was printed. Additional illustrations would have been helpful in understanding some of the more difficult areas of cognition such as the agnosias. The index is inadequate.

**Recommended audience:** This is an excellent text for any graduate student in vision research or for the clinician who wishes to gain a complete understanding of visual perception and processing. The style of each of the authors is relatively uniform, clear, and rationally structured, a feat for which the editors deserve credit.

**Critical appraisal:** Having most of the studies that have been performed on visual processing summarized in one volume makes this text a wonderful addition to the library of any neurologist, neuro-ophthalmologist, or neuroscientist. For those with limited time to track down information on visual perception and the corresponding cerebral lesions, this is the one book to have. Do not be put off by the title and think that this is just for laboratory folks. The editors have put together a marvelous text in what was obviously a Herculean endeavor.

August L. Reader, III, MD, FACS
California Pacific Medical Center
San Francisco, California

Visual Agnosia, 2nd Edition


**Scope:** This compact paperback book is the expanded work of an author whose first edition was the best comprehensive analysis of disorders of visual recognition when first published in 1990. The 14-year interval since hardback publication has seen a tremendous growth in the field due to functional neuroimaging, which has transformed cognitive neuroscience research and has been incorporated in this handy text.

**Contents:** This concise book consists of 10 well-written chapters that detail what is known about visual perception and recognition. Each chapter describes a different form of a disorder in visual recognition with successive chapters building on the information of the others. Clinical examples of each type of agnosia are taken from the literature with correlations from neuropsychology and functional neuroimaging. The book includes chapters discussing visual form agnosia, dorsal simultanagnosia, ventral simultanagnosia, pure alexia, and optic aphasia. New chapters on topographic recognition disorders, general and selective semantic memory, and expanded descriptions of prosopagnosias are added to this edition. The final chapter summarizes what is known about visual perception when all parts are functioning normally.

**Strengths:** This well-written book contains all the clinically useful information about visual agnosias as well
as background for the laboratory researcher. The clinical examples are classic for each disorder and give the reader the tools to differentiate some of the subtleties. The illustrations and figures are excellent. The use of neuroimaging and neuropathology correlations adds a distinct flavor to the theories of which pathways are involved with each deficit. The references are plentiful and pertinent. The index is adequate.

Weaknesses: It is hard to find any weakness in a book that is probably the most authoritative work on its particular subject. However, I believe that the book would be enhanced if pictures were included of the functional MRI, positron emission tomography, single photon emission computed tomography, or other neuroimaging studies pertinent to each case.

Recommended audience: Although written by a PhD neuropsychologist, this useful volume should be in the library of any clinical neurologist, neurosurgeon, or neuroophthalmologist.

Critical appraisal: This is the best available book on visual agnosias and is absolutely needed by anyone who deals with these fascinating patients.

August L. Reader, III, MD, FACS
California Pacific Medical Center
San Francisco, California

The History of Moorfields Eye Hospital. Volume III: Forty Years On


Scope: This is a comprehensive account of the past 40 years at Moorfields Eye Hospital, a world-renowned ophthalmic hospital, said to be the busiest in the Western world, and now one of the few (possibly the only) single-specialty self-governing, non-psychiatric hospital in the United Kingdom. This third volume covers only 40 years out of the 200 since John Cunningham Saunders founded The Royal London Ophthalmic from which, together with the Central London Ophthalmic and the Royal Westminster Ophthalmic, Moorfields originated. It follows Volumes I and II, by Treacher Collins (1929) and Frank Law (1975), respectively.

The first part, “A General Account,” describes the hospital’s development with particular reference to the rapidly changing political imperatives, the 40 years under consideration comprising more than two-thirds of the duration of the National Health Service.

The “Clinical, Nursing and Clinical Support Services” section deals with the hospital’s application of developments in the United States such as indirect ophthalmoscopy (by Lorimer Fison) and botulinum toxin therapy (John Lcc). Attention is drawn to the powerful influence of several ophthalmologists, including Barrie Jones, to whom the book is dedicated. Alan Bird, Noel Rice, Peter Wright, Arthur Steele, Peter Watson, John Wright, and Richard Collins. There are several references to the challenge of providing a neuro-ophthalmology service within the setting of an ophthalmic hospital.

In chapters entitled “Academe” and “The Organisation,” the author admits that research is given relatively little consideration in the belief that it would be dealt with better in the context of a history of the Institute of Ophthalmology, the research institute allied to the hospital.

Strengths: Writing about one’s peers is difficult and potentially treacherous. But Peter Leaver, who retired from Moorfields Eye Hospital in 2000, provides a balanced account in a gentle narrative format that reflects his even-handedness and has already been well-received by the Moorfields community. The relationship between Moorfields and the rest of the British ophthalmic community has not always been easy. Away from London, the worldwide reputation of Moorfields is accepted but not necessarily promoted. Near London, the relationship is often strained and sometimes hostile, especially where the political imposition of a market economy has caused difficulties for other ophthalmic units. Moorfields’ determination to survive despite the various government initiatives has often been interpreted by others as reflecting an attitude of superiority and domination, facilitated by the advantage of only having to cope with a single relatively profitable specialty. The author makes clear that it has been difficult for a relatively small, well-organized hospital restricted to ophthalmology to survive the various initiatives in health care. How difficult in comparison it has been for larger hospitals to deal with the innumerable targets set by successive governments can only be surmised, but a particular achievement of this book is the clear documentation of how healthcare in the United Kingdom has been dominated by political factors, driven to some extent by socioeconomic factors, rather than by clinical necessity.

This is a very intimate picture of life at Moorfields, encompassing even the role of porters and telephone switchboard staff. Several sections of the text are italicized to delineate stories, directly attributable or apocryphal, or quotes from interviews. Some parts are especially amusing, including the exhortation to John Hungerford, when appointed as a Consultant specializing in oncology despite no previous experience that he should not go to the United States to acquire experience because “we shall look a
laughing stock, if you do that. Get stuck in and learn as you go along!” John Hungerford did acquire the necessary skills and experience, maintaining that he had been able to do so with the benefit of an open mind.

Weaknesses: Material is repeated but, as the author notes in the Preface, this is difficult to avoid when each section is intended to be freestanding. For some readers the text may seem too introspective and self-congratulatory. The book is principally about the desire to control adult and pediatric ophthalmology services across London and the neighboring areas, advocated as improving patient care but perceived externally as ruthless expansionism. There is little about the influence of Moorfields nationally and internationally or critical analysis of achievements in the face of political necessity. Whereas at the beginning of this period of history, virtually all aspiring ophthalmologists in the United Kingdom and abroad were determined to spend time at Moorfields, the development of many high quality departments of ophthalmology outside London has reduced the flow to Moorfields. There is some reference to deficiencies, such as the slow acceptance of intraocular lenses. Those who do not understand the reluctance of the British ophthalmic community to acclaim Sir Harold Ridley’s contribution to the development of intraocular lenses will find some explanation here.

Recommended audience: The primary audience will be those who have experienced Moorfields directly, whether as a member of the medical, nursing, paramedical, clerical, or administrative staff, or even as a patient. But anyone interested in ophthalmic history will benefit from reading this book. Anyone wishing to understand the political influences on the National Health Service during the past 40 years should certainly read Part 1 for a well-written, comprehensive, and fair account.

Critical appraisal: Although written about a specific organization, this book strongly reaffirms the statement by the psychiatrist R. D. Laing (1927–1989) that “we live in a moment of history where change is so speeded up that we begin to see the present only when it is already disappearing.” For that reason, documentation of such history is crucial. It amply fulfills the author’s intention “to satisfy the curiosity of anyone who wants to know what makes Moorfields tick.” The jacket illustration of the Moorfields clock, erected to mark the hospital’s centenary on its current site and in the shape of an eye, is particularly apposite.

Paul Riordan-Eva, FRCOphth
King’s College Hospital
London, United Kingdom

Sight Unseen: An Exploration of Conscious and Unconscious Vision


Scope: In this 135-page book, the reader is introduced to a young woman who lost her sight in a tragic accident 15 years ago. We follow her extensive neuropsychologic evaluation and progress, woven into the authors’ theory of a dual visual system. “Dee” has lost the ability to recognize shape and form, yet she retains the ability to act on what she sees (picking up a coffee cup, ambulating). The authors postulate a system for action that is separate from a system for conscious vision. They proceed through testing and comparison with patients with opposite defects, concluding with support from newly available neuroimaging studies (functional MRI).

Color plates give brilliant examples of face recognition, along with anatomic correlation of areas under discussion. The chapters are in narrative form, interspersed with boxes and figures that detail the neuroscientific principles. One gets the sense this is a work in progress, as advances in neuroscience allow confirmation or refutation of the proposed theories.

Strengths: The book can be understood without extensive scientific or neurologic background. The narrative style is appealing and conveys the authors’ excitement about their topic. This book is written by consummate teachers with the ability to pass on their delight to their students.

Weaknesses: There is excessive repetition, more than is needed to get the points across. One wonders if this isn’t the result of expanding a monograph into a book.

Recommended audience: Anyone who is fascinated by brain function will enjoy this read. The text is appropriate reading for physicians, neuropsychologists, psychotherapists, and family members of patients with cognitive visual dysfunction.

This book should be read by all ophthalmology residents to broaden their perspective and also teach them that there is still a lot to be learned about how and what we see.

Critical appraisal: The authors have spectacular credentials: Goodale is Professor of Psychology at the University of Western Ontario, Canada; Milner is Professor of Applied Psychology University of Durham, Queen’s Campus, United Kingdom. They began to work together over 30 years ago in St. Andrews, Scotland. This book puts a human touch on their years of research in cognitive vision. It reminds us that there is much to be learned from our
patients, those individuals who must live with the visual problems we diagnose.

Sharon Kuritzky, MD
Amherst, NY

Atlas of Neuro-Ophthalmology


Scope: This is a color atlas covering a wide range of common and uncommon neuro-ophthalmic and orbital disorders. In this revised and updated edition, the author has compiled clinical photographs spanning greater than 20 years of his career experience. These photographs are accompanied by explanatory text, neuroimaging, anatomic illustrations, and intra-operative images.

The book is divided into two parts. The first is dedicated to the afferent visual system and covers the pupil, visual loss from both neuro-ophthalmic and non-neuro-ophthalmic causes, optic nerve disorders, and trauma. The second part focuses on the efferent visual system and includes sections on ptosis, horizontal and vertical motility dysfunction, parasellar syndromes, and orbital disorders.

Strengths: The author has strived to show the reader clinical presentations ranging from the very obvious to the very subtle. The color photographs are of high quality as is the neuroimaging. There are excellent sections on retinal disease causing unexplained visual loss as well as on papilledema and pseudotumor cerebri. The author has also included detailed surgical techniques on temporal artery biopsy, optic nerve sheath fenestration, and select strabismus procedures with accompanying diagrams. The last section on the orbit gives an extensive overview of mass lesions and inflammatory diseases which can present in both pediatric and adult populations.

Weaknesses: Numerous figures are mislabeled. The laterality seen in the clinical photograph often does not match the neuroimaging. Fundus photographs or visual fields are often reversed. There are multiple errors in the text of the legends. The pathology seen on neuroimaging and intra-operative photographs is not selectively labeled. The illustrations of cranial nerve anatomy are small and difficult to follow. The first section on the pupil is neither well-written nor well-organized. Most of the text is written freestyle with interspersed case studies and few references. The author often interjects his opinions and comments intended to be humorous clinical pearls. They are distracting.

Recommended audience: Residents as well as neurologists and ophthalmologists will find this book helpful, particularly when reviewing for board examinations. It is not intended to be a basic text for medical students or to serve as an in-depth reference for neuro-ophthalmology.

Critical appraisal: This book is a valuable atlas for those wishing to become familiar with a variety of neuro-ophthalmic disorders, with the caveat that some of the figures are mislabeled.

Rudrani Banik, MD
Albert Einstein College of Medicine
Montefiore Medical Center
Bronx, New York

Comprehensive Neurosurgery

Board Review


Scope: This is a 500-page paperback compendium of the information a neurosurgeon needs to know to pass the board examinations. Covering anatomy, physiology, pathology, radiology, neurology, neurosurgery, and critical care, the material is mostly in outline form. But the outline is dressed up with interesting nuggets of information. It is written largely by the first author, a clinical professor of neurosurgery at the University of Chicago, backed by his co-authors, another neurosurgeon, a neurologist-neurophysiologist, and a neuropathologist at the University of Chicago. The subject matter is what Dr. Citow, the first author, found important and useful in his own preparation for the boards.

Strengths: The vast knowledge base of neurosurgery is astutely reduced to a very manageable spread. Above all, the information is practical—the essence of what you must know to take care of patients. The information is also interesting, which reflects not merely the inherently fascinating doings of the nervous system, but the intelligence and teaching skill of the authors. Besides the text, there are very good tables, radiographic images, schematic illustrations, and histopathologic pictures.

Weaknesses: Outlines, even when they are fleshed out with illustrations, become a tiresome read. They are casts of characters with just a hint of the stories.

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Recommended audience: Although this book is aimed at the neurosurgeon-in-training, there is much a neuro-ophthalmologist would wish to know. When smart authors do a good job of condensing vast amounts of material, their readers may learn and remember more than if they had to wade through ponderous tracts.

Critical appraisal: A wonderful glimpse into the down-home knowledge base that a neurosurgeon-in-training has to accumulate. It is not as far afield from neuro-ophthalmology as you may think. If nothing else, this is a chance to learn the language.

Jonathan D. Trobe, MD
Kellogg Eye Center
Ann Arbor, Michigan
Visually Disabling Non-Traumatic Orbital Hemorrhage in an Anticoagulated Patient with Factor VII Deficiency

We recently evaluated a 41-year-old Hispanic woman who had developed acute vision loss in the right eye with bilateral orbital soft tissue swelling. The patient had been taking warfarin for deep vein thrombosis occurring for one week earlier and had an underlying Factor VII deficiency that was to be diagnosed later.

The patient had been found to have an International Normalized Ratio (INR) of 10 at a routine follow-up visit and was treated with prothrombin complex concentrate (PCC) containing factors II, VII, IX, and X as an alternative to using fresh frozen plasma (FFP). The INR corrected to 5.9 but dropped to 9.7 within a few hours. During this time, she complained of severe headache and manifested bilateral proptosis. Within hours, she developed marked bilateral upper eyelid swelling and ecchymosis and became unable to open her right eye.

Visual acuity was no light perception (NLP) OD and 20/50 OS with a right afferent pupil defect. Marked proptosis and hemorrhagic chemosis were present bilaterally, worse OD (Fig. 1). There was severe gaze restriction in all directions OU and intraocular pressures (IOPs) were 87 mm Hg OD and 71 mm Hg OS.

Bilateral canthotomy and cantholysis, performed at the bedside, led to drainage of blood from both orbits and improved IOP OU. The patient was then treated with topical IOP-lowering agents, intravenous acetazolamide 500 mg, and methylprednisolone 250 mg. After treatment with FFP, INR corrected to 3.3. Visual acuity quickly improved to 20/20 OS, but remained NLP OD. Ophthalmoscopy showed a central retinal artery occlusion OD. Head CT (Fig. 2) showed bilateral orbital soft tissue swelling and intracranial orbital blood on the right. The patient was to undergo right orbital decompression, but this was deferred when examination under anesthesia showed improvement in proptosis and a normal IOP. Laboratory evaluation revealed Factor VII deficiency.

Orbital hemorrhages may be caused by trauma, intraocular surgery, vascular anomalies, or rarely by pre-existing coagulopathies (1-5). Krohel and Wright (1) reported 17 cases of spontaneous orbital hemorrhage, mostly from venous anomalies, but one patient had von Willebrand disease. Outcomes were noted to be excellent in patients aged under 70 years.

Reports of hemorrhages extending into the orbit in patients with coagulation factor deficiencies include cases by Pomeranz (2) and Guirgis (3) in which evaluation revealed Factor VII deficiency and Factor IX deficiency, respectively. In both cases, the hemorrhage was believed to be precipitated by mild head trauma. Visual acuity improved from 20/200 to 20/20 after surgical orbital decompression. An early series by Rubenstein (4) of 123 cases with hemophilia found that orbital hemorrhagic complications

FIG. 1. Bilateral hemorrhagic chemosis, proptosis, and periorbital ecchymosis caused by warfarin anticoagulation superimposed on Factor VII deficiency. Arrows point to locations where canthotomy and cantholysis were performed.
FIG. 2. Axial non-contrast CT shows bilateral orbital soft tissue swelling with heterogeneous density in the right intraconal space suggestive of blood (arrow).

occurred in 25 patients, but severe spontaneous orbital hemorrhage with permanent vision loss occurred in only one patient. Chang (5) reported acute orbital hemorrhage and visual loss in two patients anticoagulated with subcutaneous heparin. Neither had pre-existing coagulopathies. Visual acuity remained counting fingers and NLP despite treatment.

This case involved Factor VII deficiency, which has been reported to cause spontaneous intracranial hemorrhage (6). However, ours may be the first reported case of non-traumatic orbital hemorrhage in the setting of warfarin anticoagulation and Factor VII deficiency.

We report it to emphasize the need to consider a clotting disorder in cases of non-traumatic hemorrhage and to recognize that proptosis and eyelid swelling may be an early sign of devastating orbital hemorrhage in a patient with a clotting disorder or treatment with anticoagulants.

Jared R. Younger, MD, MPH
John G. McHenry, MD, MPH
Department of Ophthalmology
University of Texas Southwestern
Dallas, Texas
JYoung@parknet.pmh.org

REFERENCES

The 43rd Annual Meeting of the Japanese Neuro-Ophthalmology Society
Beppu, Japan
November 11–13, 2005

The 43rd Annual Meeting of the Japanese Neuro-ophthalmology Society was held in Beppu, Japan on November 11–13, 2005. The meeting was expertly hosted and organized by Professor Kazuo Nakatsuka, MD, chair of the Department of Ophthalmology, Oita Medical University, Oita, Japan. The meeting secretary was Professor Masamoto Imaizumi, MD, also of Oita University. The meeting was attended by 372 neurologists and ophthalmologists and included 58 platform presentations, 52 posters, and several invited lectures.

The meeting was conducted in Japanese at the B Con Plaza, a modern multi-purpose conference facility with an outstanding lecture hall. Beppu, the host city, is located in the southern part of Japan, an area famous for its “onsen,” or hot spring baths. Audience participation was moderated with insightful discussion of presented papers which promoted lively interaction between audience and speakers. The posters were of high quality. A banquet reception highlighted the collegial nature of the meeting and featured the finest Japanese food.

In his special lecture presentation, Professor Yoshikazu Shinoda, Department of System Neurophysiology, Tokyo Medical and Dental University, discussed the regulation of saccadic eye movements. Visiting from the Scheie Eye Institute, University of Pennsylvania, Nicholas J. Volpe, MD, (Philadelphia, PA) delivered a lecture entitled “Optic Neuropathy Update.” In his lecture entitled “Neural Mechanisms of Generation and Suppression of Saccadic Eye Movements,” Professor Yoshikazu Shinoda and his colleagues reported on the effects of electrical stimulation of the frontal eye fields (FEF) in monkeys. The FEF are believed to be involved in the generation of saccades, but several recent lines of evidence show that the FEF is also involved in the suppression of saccades. By electrical stimulation of the FEF, Professor Shinoda and colleagues found suppression of ipsilateral and bilateral visually-guided and memory-guided saccades. Suppression of ipsilateral saccades occurred at stimulus intensities lower than those needed to elicit saccades, whereas suppression of bilateral saccades required stimulation of a localized area of the FEF. Saccadic suppression of this nature may play a role in maintaining visual fixation.

Dr. Volpe’s “Optic Neuropathy Update” lecture highlighted the current thinking concerning the pathogenesis of anterior ischemic optic neuropathy (AION) and idiopathic intracranial hypertension and emphasized the important differences in clinical profiles and treatment trial results involving patients with “western” optic neuritis/multiple sclerosis as compared to those involving patients with the “optico-spinal” form of multiple sclerosis encountered more commonly in Japan.

Several authors reported their findings using optic nerve imaging modalities and multifocal visual evoked potentials. A group at Kobe City General Hospital studying optic disc edema in various optic neuropathies using scanning laser polarimetry with variable corneal compensation (Gdx VCC) found that this technique did not always disclose findings equivalent to those found on ophthalmoscopy. A group at Kyoto University found that Gdx VCC and optical coherence tomography (OCT) showed inconsistent measurements of retinal nerve fiber layer (RNFL) thickness in patients with AION and papilledema. They concluded that these techniques may not accurately measure RNFL thickness. A group at Kobe University analyzed optic nerve heads in patients with compressive optic neuropathy and “band atrophy” using Heidelberg retinal tomography (HRT) and OCT. While the HRT analysis did not show a significant difference in disc cupping as compared with normal controls, OCT did show enlargement of the optic cup. The authors attributed the difference in results between the two modalities to an underestimation of optic disc size by HRT. Professor Atsushi Mizota and his associates at Juntendo University in Chiba applied simultaneous OCT and scanning laser ophthalmoscopy (SLO) to patients with AION and optic neuritis. There was a good correlation between ophthalmoscopic findings and SLO-OCT. They concluded that SLO-OCT could be helpful in the study of optic neuropathies. Using OCT 3, a group at Nagoya University...
compared optic nerve heads of dominant optic atrophy with those of normal tension glaucoma. The optic disc cupping was shallower in dominant optic atrophy. Based on these reports, these techniques appear promising but unready for routine clinical use.

Other presentations reported point mutations (LYS 198 polymorphism) in patients with AION and one presentation found that four out of 410 patients taking ethambutol hydrochloride developed optic neuropathy. All four of the patients developing optic neuropathy used ethambutol at a dose ranging from 16–29 mg/kg/day.

Transcorneal electric stimulation, which has been found to rescue axotomized retinal ganglion cells in rats,
was used in five patients with traumatic optic neuropathy by a research group at Osaka University (Osaka, Japan). The patients had reduced visual acuity ranging from hand movements to 20/100. All patients had improvement in visual acuity after six months.

Professor Taiji Takanashi (Department of Ophthalmology, Shimane University, Izumo, Japan) reported a rare case of akinetopsia caused by sinus thrombosis. Brain single photon emission computed tomography revealed bilateral V5 lesions. This case highlights the importance of careful history taking; otherwise one would tend to dismiss as psychogenic an odd symptom such as the inability to stop pouring water in a glass before it gets full.

A group at Inouye Eye Hospital reported two patients with hemifacial spasm who were found to have an aneurysm and a meningioma compressing the seventh nerve at its exit from the brainstem. Among 400 cases in which these authors performed MRI, only these four demonstrated brain lesions. The authors concluded that neuroimaging should be done to rule out intracranial lesions in hemifacial spasm.

The meeting included an introductory presentation concerning the upcoming meeting of the 16th International Neuro-Ophthalmology Society, to be held at Zojoji Temple in Tokyo, Japan from November 29, 2006 to December 2, 2006. The meeting will be hosted by the Inouye Eye Hospital and Professor Masato Wakakura (Tokyo, Japan).

Professor Nakatsuka, his colleagues and residents at Oita University, and the Japanese neuro-ophthalmic community are to be commended for the organization and hosting of an outstanding congress.

Atsushi Miki, MD, PhD
Division of Ophthalmology and Vision Science
School of Medicine and Dental Science
Niigata University
Niigata City, Japan

Nicholas J. Volpe, MD
Scheie Eye Institute
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

Neuro-ophthalmology fellowship training programs will be able to apply for admission to a subspecialty-wide compliance program starting in July 2006. The program is designed to provide educational standards, protection of the public, trainees, training institutions, accountability, and enforcement.

The evolution of this program is complicated. At the beginning of the 21st century, national leaders in ophthalmology expressed a concern for greater accountability of subspecialty-trained ophthalmologists. This concern led to a recommendation that ophthalmology subspecialty fellowships have American College of Graduate Medical Education (ACGME) accreditation. But that approach would have entailed a heavy bureaucratic effort, enormous cost, and loss of the ability to appoint fellows as junior faculty members. Based on these issues, a counterproposal came from a special task force of the American University Professors of Ophthalmology (AUPO) chaired by Stuart L. Fine, MD (Philadelphia, PA) that recommended voluntary guidelines for compliance with standards developed by subspecialty societies. The guidelines were based on a successful program of fellowship educational requirements conducted by the American Association for Pediatric Ophthalmology & Strabismus (AAPOS) for the last nine years.

In early 2002, AUPO formed a Fellowship Compliance Committee (AUPO FCC) made up of two voting representatives from each ophthalmic subspecialty society (except for The American Society of Ophthalmic Plastic and Reconstructive Surgery) with the charge that each society develop guidelines to assure adequate training. John L. Keltner, MD (Sacramento, CA) was appointed as the chair of the AUPO FCC. The two representatives appointed from the North American Neuro-Ophthalmology Society (NANOS) were Steven E. Feldon, MD (Rochester, NY) and John L. Keltner, MD (Sacramento, CA).

In 2004, the American Uveitis Society (AUS), with the exception of oculoplastics and orbital surgery, were added to the list of subspecialties that weregrandfathered into the program. Pediatric ophthalmology was grandfathered in because of its previous nine-year compliance process. Cornea/external disease/refractive surgery had its guidelines approved and fellowship programs began applying in July 2005. Neuro-ophthalmology and glaucoma fellowship programs became eligible in July 2006. The subspecialties of pathology, retina, and uveitis are expected to join the AUPO FCC compliance process in July 2007.

Neuro-ophthalmology fellowship programs that wish to participate must apply to the AUPO FCC at www.aupofcc.org. The applications are available on the web. The cost is $250 for programs training two fellows or less and $50 for each additional fellow beyond two.

Programs will be evaluated every three years by a web-based triennial review process and by annual web-based fellow exit surveys. Monitoring will be based on a review of submitted information supplied by the fellowship program director and by review of a confidential questionnaire completed by each graduate of a participating program. The AUPO FCC will base its assessment of compliance on minimal acceptable standards of patient visits, faculty supervision, formal teaching, and compliance with federal guidelines for being on-call as well as surgical and other appropriate logs of clinical activity. Programs in AUPO FCC compliance will be listed on the AUPO FCC Web site (www.aupofcc.org) and the AUPO SF Match Web site (www.sfmatch.org).

Steven E. Feldon, MD
Rochester, New York

John L. Keltner, MD
Sacramento, California
Upcoming Meetings

March 15–March 19, 2006
American Association of Pediatric Ophthalmology & Strabismus (AAPOS) Annual Meeting
Keystone, CO
http://www.aapos.org/displaycommon.cfm?an=1&subarticlenbr=21
Contact: aapos@aoa.org

April 1–April 8, 2006
58th Annual Meeting of the American Academy of Neurology (AAN)
San Diego, CA
http://an.aan.com
Contact: memberservices@aan.com

April 21–April 27, 2006
American Association of Neurological Surgeons Annual Meeting
San Francisco, CA
http://www.aans.org/annual/2006/default.asp
Contact: info@aans.org

April 29–May 5, 2006
44th Annual Meeting of the American Society of Neuroradiology (ASNR)
San Diego, CA
Contact: vgeisendorfer@asnr.org

April 30–May 4, 2006
The Association for Research in Vision and Ophthalmology (ARVO)
Fort Lauderdale, FL
Contact: arvo@arvo.org

May 16–May 20, 2006
15th European Stroke Conference
Brussels, Belgium
http://www.eurostroke.org
Contact: HenriC@cerebro-eurostroke.org

May 21–May 23, 2006
Society of Neurological Surgeons Annual Meeting
Durham, NC
http://www.societyns.org/meeting/index.html

May 27–May 31, 2006
16th Meeting of the European Neurological Society
Lausanne, Switzerland
http://www.akm.ch/ens2006
Contact: info@akm.ch

June 13–June 17, 2006
Canadian Congress of Neurological Sciences Annual Meeting
Montreal, Quebec
http://www.ccns.org/ccns_information/events/annual_meeting/general_info.html
Contact: web@ccns.org

June 21–June 25, 2006
48th Annual Scientific Meeting of the American Headache Society
Los Angeles, CA
http://ahsnet.org/calendar
Contact: ahsmtg@aol.com

July 2–July 7, 2006
11th International Congress on Neuromuscular Diseases
Istanbul, Turkey
http://www.icnmd2006istanbul.org
Contact: icnmd2006@fapstour.com.tr

July 8–July 12, 2006
5th Forum of European Neuroscience
Vienna, Austria
Contact: christiane.riedl@uibk.ac.at

July 12–July 15, 2006
17th International Perimetric Society Meeting
Portland, OR
http://webeye.ophth.uiowa.edu/ips/meetings.htm
Contact: cajohnso@discoveriesinsight.org

Sept. 2–Sept. 6, 2006
10th Congress of the European Federation of Neurological Societies
Glasgow, UK
http://www.kenes.com/efns2006
Contact: efns96@kenes.com

Sept. 9–Sept. 16, 2006
XVIth International Congress of Neuropathology
San Francisco, CA
http://www.icn2006.org

European Association for Vision and Research (EVER)
Vilamoura, Portugal
http://www.ever.be
Contact: ever@ever.be
Oct. 7–Oct. 12, 2006  
Congress of Neurological Surgeons 56th Annual Meeting  
Chicago, IL  
http://www.neurosurgeon.org/meetings/2006/index.asp  
Contact: cns@itsmeetings.com

Oct. 8–Oct. 11, 2006  
131st Annual Meeting of the American Neurological Association  
Chicago, IL  
http://www.anэuroa.org  
Contact: Julieratzloff@llmsi.com

36th Annual Meeting of the Society for Neuroscience  
New Orleans, LA  
http://web.sfn.org  
Contact: info@sfn.org

Oct. 26–Oct. 29, 2006  
Joint World Congress on Stroke  
Cape Town, South Africa  
Contact: stroke2006@kenes.com

Oct. 29–Nov. 3, 2006  
XVII International Congress of Eye Research  
Buenos Aires, Argentina  
http://www.icer2006.com  
Contact: icer_2006@yahoo.com

Nov. 11–Nov. 14, 2006  
Annual Meeting of the American Academy of Ophthalmology (AAO)  
Las Vegas, NV  
http://www.ao.org/aoa/annual_meeting  
Contact: meetings@aoa.org

Nov. 29–Dec. 1, 2006  
16th International Neuro-Ophthalmology Society Meeting (INOS)  
Tokyo, Japan  
http://www.inos2006.jp  
Contact: inos@inouye-eye.or.jp

Dec. 2, 2006  
Joint Meeting of the 44th Japanese Neuro-Ophthalmology Society and 3rd Asian Neuro-Ophthalmology Society  
Tokyo, Japan  
http://shinkeiganka.com

Feb. 10–Feb. 15, 2007  
Snowbird, UT  
http://www.nanosweb.org/meetings/index.htm  
Contact: info@nanosnet.org

April 28–May 5, 2007  
59th Annual Meeting of the American Academy of Neurology  
Boston, MA  
http://www.aan.com  
Contact: dkukla@aan.com

May 26–May 29, 2007  
European Neuro-Ophthalmology Society (EUNOS)  
Istanbul, Turkey  
http://www.eunos2007.org  
Contact: info@eunos2007.org

June 9–June 12, 2007  
European Society of Ophthalmology (Societas Ophthalmologica Europaea)  
Vienna, Austria  
http://www.soe2007.org  
Contact: secretariat@soevision.org

June 24–July 3, 2008  
World Ophthalmology Congress  
Hong Kong, China  
http://www.icoph.org/congress/index.html/hongkong

July 12–July 17, 2007  
IBRO World Congress of Neuroscience  
Melbourne, Australia  
http://www.ibro2007.org  
Contact: ibro2007@sallyjayconferences.com.au