EDITORIAL
249 Does Early Immunotherapy Reduce the Conversion of Ocular Myasthenia Gravis to Generalized Myasthenia Gravis?
Mark J. Kupersmith

ORIGINAL CONTRIBUTIONS
251 Immunotherapy of Ocular Myasthenia Gravis Reduces Conversion to Generalized Myasthenia Gravis
Jared Mee, Mark Paine, Edward Byrne, John King, Katrina Reardon, and Justin O'Day

256 Interferon-α–Associated Bilateral Simultaneous Ischemic Optic Neuropathy
Yoav Vardizer, Yifat Linhart, Anat Loewenstein, Hanna Garzozi, Niall Mazawi, and Anat Kesler

260 Laser Pointer Visual Field Screening
Michael S. Lee, Laura J. Balcer, Nicholas J. Volpe, Grant T. Liu, Gui S. Ying, and Steven L. Galetta

264 Posner-Schlossman Syndrome and Nonarteritic Anterior Ischemic Optic Neuropathy
Inci Irak, Bradley J. Katz, Norm A. Zabristkathe, and Paul L. Zimmerman

PHOTO ESSAYS
272 Siegrist Streaks in Giant Cell Arteritis
Dustin J. Coupal and Anil D. Patel

274 Retinal Vascular Abnormalities in Neurofibromatosis Type 1
Panagiotis Karadimas, Efterpi Hatzispasou, and Evrydiki A. Bouzas

276 Rocky Mountain Spotted Fever as a Cause of Macular Star Figure
Michael S. Vaphiades

STATE OF THE ART
279 The Multifocal Visual Evoked Potential
Donald C. Hood, Jeffrey G. Odel, and Bryan J. Winn

LEGACY
290 Adelbert Ames and the Dartmouth Eye Institute
Susan M. Pepin

(continued on next page)
NEURO-OPHTHALMOLOGY AT LARGE

298 Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO), Fort Lauderdale, Florida, May 4-9, 2003

Swaraj Bose


Michael C. Brodsky

NANOS News

306 Dennis R. Anderson

307

308 CALENDAR

Howard D. Pomeranz

309 ERRATUM

310 ACKNOWLEDGMENT OF REVIEWERS

311 AUTHOR INDEX

314 SUBJECT INDEX

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Does Early Immunotherapy Reduce the Conversion of Ocular Myasthenia Gravis to Generalized Myasthenia Gravis?

Mark J. Kupersmith, MD

Myasthenia gravis (MG), an autoimmune disorder affecting those of all ages, has a prevalence of approximately 20/100,000. MG limited to the extracocular and levator palpebrae muscles ("ocular myasthenia gravis," OMG) occurs about half as often, with a prevalence of 12/100,000 (1). Although advances in laboratory neurophysiology and molecular neurobiology have provided insights into the pathophysiology of MG, little progress has occurred in the treatment of OMG. Clinicians remain mired in the debate as to whether OMG merits the risk of immunomodulatory therapy (2,3). Diplopia and ptosis often are not considered debilitating, and despite the knowledge that 40–50% of patients with OMG will develop generalized myasthenia gravis (GMG), 90% of them within 2 years, many physicians believe that pyridostigmine therapy is sufficient until more serious disease develops. They suggest that delaying immunomodulatory therapy will provide the same benefit as earlier treatment.

In this issue, the study of Mee et al. (4) joins the growing number of retrospective investigations suggesting that early immunomodulatory treatment (5–7), particularly with corticosteroids, can delay and possibly reduce the frequency of progression of OMG to GMG. The authors retrospectively analyzed the charts of 34 patients with OMG and abnormal serum acetylcholine receptor antibody to avoid inclusion of non-myasthenic causes of ophthalmoparesis (4). In doing so, they have chosen patients with the highest risk of developing GMG (7). The edrophonium test was positive in 86% of patients tested, which is slightly lower than the previously reported rate of 96%, (7) possibly due to methodological differences (8). Nineteen (86%) of 22 patients treated with pyridostigmine alone developed GMG, whereas only 2 (16.7%) of 12 patients receiving immunomodulatory therapy (corticosteroids, azathioprine, thymectomy, individually or in combination) developed GMG during a follow-up period of approximately 90 months. The selected cohort may not accurately reflect the entire population with OMG, given that the conversion rate to GMG in the pyridostigmine group was higher than has been reported in larger studies (7,9,10). One explanation for these differences is that patients with asymptomatic GMG, who might have been uncovered with a detailed clinical neuromuscular examination, were included. They were bound to eventually demonstrate GMG signs and symptoms. Additionally, the authors eliminated several patients who developed GMG within 6 months of immunomodulatory therapy, introducing potentially favorable bias toward immunomodulatory therapy.

One approach to modulate the immune response in myasthenia gravis has been to perform thymectomy. In the current study, five patients without thymoma, including two who were not included in the data analysis, underwent thymectomy (4). Although thymectomy has been reported to restore vision and prevent GMG in small case series, typically the surgery has been performed late in the illness when the risk of developing GMG was low. In
TABLE 1. Criteria for diagnosing ocular myasthenia gravis

1. Ptosis in one or both upper lids not due to local lid disease, preferably that fatigues and recovers with rest.
2. Extraocular muscle weakness in one or both eyes not conforming to the innervation pattern of the third cranial nerve or to a restrictive myopathy. If an abduction deficit is the only finding, there must be obvious fatigability, recovery with rest, or a positive edrophonium test.
3. Weakness of one or both orbicularis oculi muscles but not in other muscles of the head or neck.
4. No pupillary abnormality except from prior ocular disease or surgery.
5. A plus B, C, D or E must be present:
   A. Fatigue of the affected muscle with worsening of the ptosis after upward gaze lasting for 30 to 60 seconds or worsening of monocular duction after 60 to 120 seconds of gaze in the direction of the agonist muscle.
   B. Recovery of the upper lid ptosis almost to normal after 30 seconds to 10 minutes of eyelid closure. Recovery of the monocular ductional deficit after 120 to 180 seconds of gaze in the direction of the antagonist muscle.
   C. A positive edrophonium test.
   D. Abnormal repetitive stimulation electromyography with a minimum decrement of 10%.
   E. Abnormal serum acetylcholine receptor binding antibody level.

REFERENCES

Immunotherapy of Ocular Myasthenia Gravis Reduces Conversion to Generalized Myasthenia Gravis

Jared Mee, MB, BS, Mark Paine, MB, BS, Edward Byrne, MD, DSC, John King, MB, BS, Katrina Reardon, MB, BS, PhD, and Justin O’Day, MB, BS

Abstract

Background: Several retrospective studies have suggested that immunotherapy, including prednisolone, azathioprine and thymectomy, reduces progression of ocular myasthenia gravis to generalized myasthenia gravis. This study examines the effect of immunotherapy on generalization rates in ocular myasthenia patients who are acetylcholine receptor (AChR) antibody-positive.

Methods: Retrospective record review of 34 patients from three university-based hospitals with neurology and neuro-ophthalmology services in Australia. In all patients, positive AChR antibodies were recorded, the initial symptoms were purely ocular, and all had at least 2 years of follow-up. The patients who developed generalized myasthenia gravis were compared with those who remained purely ocular.

Results: There were 21 patients who developed generalized myasthenia gravis. Of these 21, only 2 (9.5%) had received prior immunotherapy. Among the 13 patients whose symptoms remained purely ocular, 10 (76.9%) had received prior immunotherapy.

Conclusions: In this study, most of the patients who progressed from ocular myasthenia to generalized myasthenia had not received prior immunotherapy. This study adds weight to the call for a prospective trial of early immunotherapy in patients with ocular myasthenia.


Myasthenia gravis is an autoimmune condition in which antibodies to the acetylcholine receptor (AChR) cause weakness of somatic musculature. In ocular myasthenia, the weakness is limited to the extraocular, levator, and orbicularis oculi muscles. Progression to generalized myasthenia occurs in about 50%, usually within 2 or 3 years (1,2). Ocular myasthenia is treated according to symptoms with pyridostigmine and immunotherapies such as prednisolone, azathioprine, and thymectomy. Prednisolone and azathioprine doses are minimized to limit side effects. Thymectomy is used to treat younger patients with thymic enlargement noted on computed tomography (CT).

Studies by Sommer et al (3) and Kupersmith et al (4) suggest that immunotherapy may reduce the risk of generalization in ocular myasthenia. Studies of ocular myasthenia can, however, be compromised by vague diagnostic criteria in seronegative patients, inadequate follow-up times, or selection bias from the inclusion of patients presenting with many years of purely ocular symptoms. In this study, we reviewed 34 AChR-positive patients to find the effect of immunotherapy on generalization.

METHODS

Patients were identified from a central database of AChR antibody tests. Ethical approval was obtained from all three involved hospitals to access the AChR database and to view medical records with consent from the patient. All patients had been examined by neurologists or neuro-ophthalmologists between January 1990 and January 2002. Most patients had presented between 1998 and 2002.

Using the AChR database and medical records, we found 44 patients who were AChR-positive on first or subsequent testing and whose initial symptoms were purely ocular. We excluded four patients who had less than 2 years of follow-up from their initial symptoms, to reduce selection bias, three patients who had more than 2 years of ocular symptoms before their first presentation were also excluded. Three patients were excluded because it could not be determined whether they had received significant immunotherapy. One excluded patient had only 1 month of prednisolone and the other two patients had developed systemic myasthenia at 3 and 6 months post-thymectomy, given that this procedure generally takes 6 months to 3 years to have its effect.

The treatment approach of different physicians varied slightly. The general approach was to treat first with an anticholinesterase and then introduce prednisolone 25mg...
daily if the symptoms were troublesome. If the prednisolone could not be tapered over the following months, then azathioprine might be prescribed. Videoscopic thymectomy was considered in patients with an enlarged thymus on CT.

Generalization was determined from the patient records, based on the opinion of the treating neurologists or neuro-ophtalmologists.

Antibodies to AChR were measured by radioimmunoassay according to the method of Vincent and Newsom-Davis (5). The source of antigen was receptor protein from cell line TE671, a subline of the rhabdomyosarcoma cell line. TE671-sourced AChR receptors labeled with $^{125}$I Alpha bungarotoxin were incubated with patient specimens and then immunoprecipitated with anti-human IgG. After centrifugation, the labeled AChR autoantibody-bound complex was counted in a gamma counter.

**RESULTS**

**Patient Characteristics**

There were 34 AChR-positive patients with only ocular myasthenic manifestations on initial evaluation. These included diplopia or ptosis that were diurnal or worse after exercise, weak orbicularis oculi function with fatigability, and Cogan’s lid twitch. Age at onset ranged from 18 to 87 years and averaged 55.1 years. Nineteen patients were male and 15 were female. Three patients had concomitant thyroid disease. Twenty-three patients underwent single-fiber electromyography (SFEMG) of orbicularis oculi, frontalis, or extensor digitorum communis; 16 (70%) of these tests were positive. Of 21 patients who underwent intravenous edrophonium chloride (Tensilon) testing, 18 (86%) were positive. All five patients who underwent the ice test were positive. Two AChR-positive patients had clinical features of ocular myasthenia but negative Tensilon and SFEMG tests.

The patients were divided into two groups. The first group contained 21 patients who progressed to generalized myasthenia (“generalized group”); the second group contained 13 patients whose manifestations remained purely ocular at final follow-up (“ocular group”). The two patient groups were compared (Table 1). There were 11 men and 10 women in the generalized group, and 8 men and 5 women in the ocular group. The time from initial symptoms to first presentation was 7.90 ± 7.85 months in the generalized group and 5.58 ± 7.13 months in the ocular group. Follow-up time was 50.38 ± 43.18 months in the generalized group and 50.61 ± 33.84 months in the ocular group. Age at onset averaged 48.62 ± 18.42 years in the generalized group and 65.46 ± 12 in the ocular group. This difference in age was statistically significant (t-test, P = 0.0029). AChR antibody titer averaged 51.65 in the generalized group and 50.87 in the ocular group. SFEMG tests were positive more frequently in the generalized group (12/16, or 75%) than in the ocular group (4/8, or 50%). This difference was not statistically significant (P = 0.36, Fisher exact test).

**Treatment Characteristics**

There were 21 patients who progressed from ocular to generalized myasthenia; only 2 (9.5%) of these patients had received immunotherapy prior to generalizing (Fig. 1). One patient generalized 15 months after thymectomy and the other 14 months after being started on treatment with prednisolone. The remaining 19 patients had received pyridostigmine or no treatment prior to generalization (Table 2). Ten (76.9%) of the 13 patients who remained purely ocular had received immunotherapy (Fig. 1). All 10 had received prednisolone. The maximum dose received was

<table>
<thead>
<tr>
<th>TABLE 1. Comparison of generalized and ocular myasthenic patient groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received immunotherapy</td>
</tr>
<tr>
<td>No prior immunotherapy</td>
</tr>
<tr>
<td>Average age (years)</td>
</tr>
<tr>
<td>Male/female</td>
</tr>
<tr>
<td>Prior symptom duration* (months)</td>
</tr>
<tr>
<td>Follow-up time** (months)</td>
</tr>
<tr>
<td>Average AChR titer</td>
</tr>
</tbody>
</table>

* The average time from symptom onset to first presentation.
** The average time from symptom onset to last follow-up appointment.

**FIGURE 1.** Outcomes in 34 patients with acetylcholine receptor antibody-positive myasthenia gravis presenting with purely ocular manifestations.
Ocular Myasthenia: Immunotherapy Reduces Generalization


### TABLE 2. Patients who progressed to generalized myasthenia. Clinical features and treatment

<table>
<thead>
<tr>
<th>Age/gender</th>
<th>Symptom duration* (months)</th>
<th>AChR**</th>
<th>Pyridostigmine therapy</th>
<th>Immunosuppressive therapy</th>
<th>Time to generalization (months)</th>
<th>Follow-up (months)</th>
<th>Adverse effects of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>77/M</td>
<td>16</td>
<td>46</td>
<td>No</td>
<td></td>
<td>24</td>
<td>30</td>
<td>Cushing's</td>
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<tr>
<td>58/M</td>
<td>4</td>
<td>6.9</td>
<td>Yes</td>
<td></td>
<td>23</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>47/M</td>
<td>8</td>
<td>47</td>
<td>No</td>
<td></td>
<td>8</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>39/F</td>
<td>1</td>
<td>47</td>
<td>Yes</td>
<td>Prednisolone</td>
<td>40</td>
<td>183</td>
<td></td>
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<tr>
<td>31/F</td>
<td>4</td>
<td>110</td>
<td>Yes</td>
<td></td>
<td>20</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>45/M</td>
<td>12</td>
<td>91</td>
<td>Yes</td>
<td></td>
<td>22</td>
<td>122</td>
<td></td>
</tr>
<tr>
<td>66/M</td>
<td>7</td>
<td>69</td>
<td>Yes</td>
<td></td>
<td>8</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>50/M</td>
<td>24</td>
<td>8</td>
<td>Yes</td>
<td>Thymectomy</td>
<td>29</td>
<td>64</td>
<td></td>
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<tr>
<td>70/M</td>
<td>2</td>
<td>92</td>
<td>Yes</td>
<td></td>
<td>18</td>
<td>73</td>
<td></td>
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<tr>
<td>18/F</td>
<td>1</td>
<td>22</td>
<td>Yes</td>
<td></td>
<td>7</td>
<td>8</td>
<td></td>
</tr>
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<td>74/M</td>
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<td>71</td>
<td>Yes</td>
<td></td>
<td>31</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>39/F</td>
<td>6</td>
<td>77</td>
<td>Yes</td>
<td></td>
<td>1</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>62/M</td>
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<td>3.6</td>
<td>No</td>
<td></td>
<td>3</td>
<td>9</td>
<td></td>
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<tr>
<td>44/F</td>
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<td></td>
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<td>20/M</td>
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<td>Yes</td>
<td></td>
<td>55</td>
<td>60</td>
<td></td>
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<tr>
<td>20/F</td>
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<td>140</td>
<td>No</td>
<td></td>
<td>12</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>59/M</td>
<td>4</td>
<td>4.4</td>
<td>No</td>
<td></td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>21/M</td>
<td>12</td>
<td>8.4</td>
<td>No</td>
<td></td>
<td>12</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>50/F</td>
<td>24</td>
<td>70</td>
<td>No</td>
<td></td>
<td>21</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>45/F</td>
<td>5</td>
<td>74</td>
<td>No</td>
<td></td>
<td>59</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>66/F</td>
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<td>0.4</td>
<td>No</td>
<td></td>
<td>5</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

* From initial symptoms to first presentation.
** Acetylcholinesterase Receptor Antibody titer.

25mg/d for eight. The other two patients had had a maximum dose of 15mg/d and 37.5mg/d. The treatment duration ranged from 1 to 92 months (average 33.5 months) and 9 patients had received more than 12 months of treatment. The patient who received only 1 month of prednisolone had been treated with azathioprine for 3 months and underwent thymectomy for thymoma soon after initial presentation. Four other patients also received azathioprine and two underwent thymectomy (Table 3). Three patients in the ocular group received no immunotherapy at all.

The difference between the proportion of those who generalized after receiving immunotherapy versus no immunotherapy was statistically significant (P = 0.00011, Fisher exact test) (6). Overall, 61.8% of the patients developed generalized myasthenia gravis. Of those who generalized, 76% did so by 2 years. The generalized manifestations developed from 3 to 59 months after the initial ocular manifestations (average 19.4 ± 16.3 months).

Adverse treatment effects were noted in four patients. Two patients developed a Cushingoid appearance, one developed diabetes, and another became obese.

**DISCUSSION**

We have studied 34 AChR-positive patients with over 2 years' follow-up and less than 2 years of ocular myasthenic manifestations prior to presentation. Of 21 who generalized, only 2 (9.5%) had received immunotherapy prior to generalization. By comparison, of the 13 who remained ocular, 10 (76.9%) had received immunotherapy. The generalized and (purely) ocular groups were similar in duration of symptoms prior to first presentation, and in follow up times. The ocular group was, on average, 15 years older. This may suggest that older patients are less likely to generalize. However, previous authors have found no association between age of onset and generalization (3,7). In one study, patients aged over 50 years actually had a higher risk of generalization and respiratory crisis (8). This is opposite to the trend in our study.

Some retrospective studies have indicated that immunotherapy might lower the rate of generalization, but the evidence is inconclusive. Kupersmith et al (4) treated 32 ocular myasthenia patients with prednisolone and found that only 9% generalized. Most patients presented within a
TABLE 3. Patients who did not progress to generalized myasthenia (ocular group). Clinical features and treatment

<table>
<thead>
<tr>
<th>Age/gender</th>
<th>Symptom duration (months)*</th>
<th>Prednisolone dose range (mg)</th>
<th>Duration of prednisolone therapy (months)</th>
<th>Adverse effects of prednisolone therapy</th>
<th>Duration of azathioprine therapy (months)</th>
<th>Thymectomy (months)</th>
<th>Follow-up (months)</th>
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</thead>
<tbody>
<tr>
<td>56/M</td>
<td>5</td>
<td>81</td>
<td>5–25</td>
<td>43</td>
<td>Cushing's obesity</td>
<td>None</td>
<td>49</td>
</tr>
<tr>
<td>51/F</td>
<td>12</td>
<td>200</td>
<td>6–25</td>
<td>14</td>
<td>None</td>
<td>5</td>
<td>24</td>
</tr>
<tr>
<td>74/M</td>
<td>1</td>
<td>14</td>
<td>2–20</td>
<td>92</td>
<td>None</td>
<td>None</td>
<td>153</td>
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<tr>
<td>53/M</td>
<td>24</td>
<td>90</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>5</td>
<td>26</td>
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<tr>
<td>87/F</td>
<td>&lt;1</td>
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<td>15</td>
<td>1</td>
<td>None</td>
<td>5</td>
<td>33</td>
</tr>
<tr>
<td>87/F</td>
<td>&lt;1</td>
<td>27</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>5</td>
<td>67</td>
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<tr>
<td>67/M</td>
<td>5</td>
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<td>11–25</td>
<td>50</td>
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<td>32</td>
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<tr>
<td>63/F</td>
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<td>2–25</td>
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<td>None</td>
<td>48</td>
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<tr>
<td>87/F</td>
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<td>5.6</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>5</td>
<td>40</td>
</tr>
<tr>
<td>59/M</td>
<td>12</td>
<td>5.8</td>
<td>1–25</td>
<td>31</td>
<td>None</td>
<td>None</td>
<td>52</td>
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<tr>
<td>74/M</td>
<td>1</td>
<td>39</td>
<td>10–37</td>
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<td>24</td>
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<tr>
<td>55/M</td>
<td>2</td>
<td>26</td>
<td>5–25</td>
<td>18</td>
<td>None</td>
<td>None</td>
<td>46</td>
</tr>
<tr>
<td>59/F</td>
<td>&lt;1</td>
<td>36</td>
<td>12–25</td>
<td>29</td>
<td>diabetes</td>
<td>24</td>
<td>4</td>
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</table>

* From initial symptoms to first presentation.
** Acetylcholinesterase Receptor Antibody titer.
*** Time from initial symptoms to thymectomy.

Few months of symptom onset and all had at least 2 years' follow-up. Only 10 of 28 were seropositive and 31 of 32 had a positive Tensilon test. Sommer et al (3) reviewed 78 ocular myasthenics. Among 50 patients receiving immunotherapy, only 12% generalized, whereas among 28 patients who had not received immunotherapy, 64% generalized. The diagnoses were made an average of 40 months after symptom onset, so that this study may have selected late-presenting patients who were unlikely to generalize. In the Sommer et al (3) study, there was no analysis of the differences between the groups. Schimm et al (9) performed thymectomy on 18 ocular myasthenics at an average of 40 months after symptom onset. All improved, three achieved full remission, and none generalized. However, at 40 months from symptom onset, few ocular myasthenics would be expected to generalize even without treatment. Immunosuppressants were used in parallel and may have contributed to the results. Oosterhuis (10) reviewed patients managed from 1925 to 1965 without immunotherapy and found that 69% developed generalized myasthenia. This is a higher rate than in more recent studies of patients who do receive immunotherapy; for example, Sommer et al (3) found a 31% conversion rate.

Early immunotherapy might be expected to prevent generalization of ocular myasthenia. Prednisolone has been shown to increase the incidence of remission and symptomatic improvement. (2) Myasthenia is an autoimmune condition and prednisolone suppresses antibody production (11) and specifically T lymphocyte responses (12).

In a study of over 750 ocular myasthenics, Grob et al (2) found that 66% of the patients developed generalized disease. Of the patients whose symptoms were purely ocular after 1 year, 84% remained purely ocular. Perhaps early immunotherapy in the first 1 to 2 years might get patients through this period without having them generalize.

It may be time for a prospective trial of early prednisolone use or thymectomy to prevent generalization of ocular myasthenia. Such a trial will expose patients to increased treatment side effects and risks, so existing studies need to indicate a likely benefit to the patient. A prospective trial would also require definite diagnoses in all patients.

The existing retrospective studies are few in number and weakened by the inclusion of patients presenting with several years of purely ocular symptoms who are therefore unlikely to generalize no matter what treatment they receive. If follow-up times are short or unstated, patients may be counted as having remained ocular yet generalize after the study period has ended.

Another weakness of the existing studies is the inclusion of many seronegative patients, some of whom may not have myasthenia. The lack of a gold standard diagnostic test makes it difficult to get a definite diagnosis in AChR-negative ocular myasthenia patients. The Tensilon test and SFEMG are not entirely specific for myasthenia (13,14,15). Depending on what diagnostic criteria are used,
studies with a large proportion of seronegative patients are likely to contain varying numbers of patients with the wrong diagnosis and this will influence the quoted generalization rates. If AChR antibodies, which are highly specific (99%) for myasthenia (13,16) are present, then the diagnosis is fairly certain.

The strengths of our study are that the diagnosis of ocular myasthenia is fairly certain in all patients and that latency times from symptom onset to presentation and follow-up times are appropriate and comparable in the two patient groups. However, the study has the inherent weaknesses of a retrospective review. The age difference between the two groups may also be a confounding factor. Even so, this study is sufficiently robust to provide strong evidence to support a prospective trial of early immunotherapy in ocular myasthenia.

REFERENCES

Interferon-α–Associated Bilateral Simultaneous Ischemic Optic Neuropathy

Yoav Vardizer, MD, Yifat Linhart, MD, Anat Loewenstein, MD, Hanna Garzozi, MD, Nail Mazawi, MD, and Anat Kesler, MD

Abstract: The authors describe one patient with essential thrombocytosis and one with chronic hepatitis C infection who developed bilateral simultaneous anterior ischemic optic neuropathy within 3 months of starting treatment with interferon-α. One patient had several typical risk factors for conventional AION; the other did not. These cases are the fourth and fifth reported examples of this phenomenon. Interferon-α treatment may cause or aggravate the risk of developing anterior ischemic optic neuropathy. Vulnerable patients should be advised of this potential complication, assisted in reducing risk factors, and monitored for optic nerve and retinal vascular complications.

CASE REPORTS

Case 1

A 61-year-old man was admitted due to painless visual loss in the OD. Medical history included insulin-dependent diabetes mellitus, hypertension, ischemic heart disease, and hypercholesterolemia. He also had essential thrombocytosis treated for the past 2 years with anagrelide HC1 (Agrylin) and hydroxyurea (Hydrea). Three months before the patient's hospitalization, treatment was changed to 3,000,000 IU of interferon-α four times weekly.

Visual acuity was 20/100 OD and 20/200 OS. An afferent pupillary defect was present in the OS. Fundus examination of the OS revealed a swollen disc and splinter hemorrhages temporal and superior to the optic disc. The right fundus demonstrated flame-shaped hemorrhages temporal to the optic disc (Fig. 1). Visual field examination disclosed inferonasal nerve fiber bundle defects in both eyes (Fig. 2).

The platelet count was 394,000/µL. Other blood examination findings were within normal values. Treatment with aspirin 300 mg/day was initiated.

Two months later, the patient developed a sudden further decline in vision in the OD. His best-corrected visual acuities were unchanged, but visual field examination showed progression of the nerve fiber bundle defects in both eyes (Fig. 3).

The erythrocyte sedimentation rate was 20 mm/h. Orbital ultrasonography and brain computed tomography...
Interferon-Associated AION

FIG. 1. Case 1: Fundi at presentation, showing a swollen optic disc OS and bilateral peripapillary splinter hemorrhages.

FIG. 2. Case 1: Visual fields at presentation, showing inferior nerve fiber bundle defects.

FIG. 3. Case 1: Visual fields 2 months after presentation, showing progression of nerve fiber bundle defects.

findings were within normal limits. Interferon-α treatment was discontinued, as it was presumed to be the cause of these defects. Seven months after the first examination, optic disc pallor supervened and visual fields remained unchanged.

Case 2

A 44-year-old man underwent an ophthalmic examination after waking up the same morning with a painless left inferior visual field defect. The patient was a hepatitis C virus (HCV) carrier, probably as a result of a childhood appendectomy during which he received a blood transfusion. Two and a half months prior to the ophthalmologic examination, he had started a clinical trial of interferon-α polyethylene glycol. The addition of polyethylene glycol to the interferon enables prolongation of the substance's half-life, reduces the number of injections needed per treatment, and thereby improves compliance.

Visual acuity was 20/30 OD, 20/80 OS. There was left relative afferent pupillary defect. Fundus examination of the OD revealed pallid edema of the optic nerve head with splinter hemorrhages and cotton wool spots. In the OS disc, there was optic disc edema, more elevated than in the right, with splinter hemorrhages on the nasal side, and a few cotton wool spots at the edge of the edema (Fig. 4). Visual field examination demonstrated defects suggestive of inferior nerve fiber bundle defects in both eyes (Fig. 5), worse in the OS. Neurologic assessment was otherwise normal.

Standard blood study results were normal, including erythrocyte sedimentation rate (29), white blood cell count (3300 with relative lymphopenia [16%]), hemoglobin (13.5 mg%), prothrombin time, partial thromboplastin time, protein S, protein C, antithrombin III, antiphospholipid Ab, methyltetrahydrofolate reductase, hypercoagulability indices, antinuclear antibody, venereal disease research laboratory titer, and cryoglobulins. Thyroid-stimulating hormone was on the upper edge of normal values; other thyroid function test results were normal.

Lumbar puncture had an opening pressure of 80 mm water. Cranial and orbital computed tomography findings were normal. Fluorescein angiography demonstrated late optic disc leakage with no retinal pathology. Interferon-α polyethylene glycol was discontinued.

Two days later, the patient noted a black shadow obscuring his right visual field. Visual acuity was 20/60 OD, 20/80 OS. The relative afferent pupil defect had changed from the left to the OD. Fundus examination in the OD showed enlargement of the optic nerve edema. Visual field demonstrated progression of the field defects in the OD (Fig. 6).

The patient was treated with intravenous methylprednisolone 1 g/d for 3 days, with tapering of prednisone over the next 14 days with no apparent improvement. Over the next 2 months, visual acuities improved to 20/30 in both

FIG. 4. Case 2: Fundi at presentation, showing swollen discs with splinter hemorrhages.
eyes without any change in the visual field defects. Three months later, fundus examination demonstrated optic disc pallor in both eyes.

**DISCUSSION**

We describe two patients undergoing treatment with interferon-α who developed bilateral simultaneous optic neuropathy within 3 months of starting this medication. Case 1 had established risk factors for conventional AION, including diabetes, hypertension, ischemic heart disease, and hypercholesterolemia. However, we believe that interferon-α treatment may have been a contributing factor, given that conventional AION very rarely develops simultaneously in both eyes (8). Furthermore, interferon-α has been implicated in vascular retinopathy (5) in patients with diabetes and hypertension. The contribution of the patient's essential thrombocytosis, known to predispose to retinal vascular occlusions, is unknown (9-11).

Case 2 had none of the systemic risk factors for conventional AION. We doubt that the HCV alone precipitated AION. In patients with chronic HCV infection, optic neuritis has been reported in only one patient who was not previously treated with interferon-α (12). This patient had several signs related to systemic vasculitis, including purpura and cryoglobulinemia. The authors attributed these features to HCV infection. Because our patient did not have systemic symptoms of vasculitis, we had ruled out essential mixed cryoglobulinemia, and because corticosteroids did not reverse the optic neuropathy, it is unlikely that the HCV caused the AION.

Alternatively, there is evidence that ties AION to interferon-α treatment. Three reported cases of AION (6,7) have occurred within 1 week to 3 months of starting interferon-α treatment in patients who lacked typical risk factors for AION. Purvin (6) suggested involvement of the posterior ciliary arteries rather than the retinal vessels as a possible cause for AION. Lohmann (7) postulated that interferon-α is able to produce autoantibodies and subsequently cause deposition of immune complexes in the small retinal or optic nerve arteries. Interferon-α is also able to stimulate other cytokines that can cause an inflammatory reaction of the blood vessels that might subsequently lead to ischemia (6,7,13).

Although Case 2 suffered continued deterioration of vision after discontinuation of interferon-α therapy, this could have been due to the long half-life of the polyethylene glycol variant. The continued deterioration stands in contrast to other patients described, who stabilized or even improved (14) after discontinuation of interferon-α treatment.

In view of the possible poor visual outcome associated with interferon-α treatment, we suggest that patients who are candidates for this treatment be assessed beforehand for crowded discs and systemic risk factors for conventional AION. It is also important to examine patients during treatment, because some patients who have developed interferon-α-associated retinopathy are asymptomatic, and retinal changes in the reversible phase can be detected. We recommend ophthalmic screening that includes baseline and follow-up examinations every 3 to 4 months (15).

**REFERENCES**

Laser Pointer Visual Field Screening

Michael S. Lee, MD, Laura J. Balcer, MD, MSC.E., Nicholas J. Volpe, MD, Grant T. Liu, MD, Gui S. Ying, MS, and Steven L. Galetta, MD

Background: Sensitivity of confrontation visual field (CVF) screening is low unless defects are significant. We compared the sensitivity of laser pointer visual field screening (LVF) with conventional CVF for identifying eyes with abnormal automated perimetry.

Methods: Ninety consecutive patients presenting for HVF prospectively underwent a masked comparison of CVF and LVF testing (175 eyes) from April to May 2000. LVF was performed using a laser pointer target projected onto a tangent screen. Points were tested in random fashion on either side of the vertical and horizontal meridians, near central fixation, around the blind spot, and in each quadrant. Single and double simultaneous finger counting was used to test CVF.

Results: LVF demonstrated significantly greater sensitivity as compared with CVF (73% versus 31%, \(P = 0.001\)) in identifying field defects found on HVF. Specificities for LVF and CVF were 82% and 99%, respectively. The average testing times per eye were 0.5 minute for CVF, 1.5 minutes for LVF, and 8.0 minutes for HVF.

Conclusions: In this cohort, laser visual field testing was significantly more sensitive than confrontation testing. It may represent an effective, time-efficient tool for visual field screening.

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fixating on the examiner’s nose, the patient subjectively identified any parts of the examiner’s face that appeared to be dim or “missing.” Single and double simultaneous finger counting was used in each quadrant to assess peripheral fields.

LVF was performed using a commercially purchased laser pointer (Beta Electronics, OH). The red laser beam had a wavelength of 633–680 nm (Class IIIa Laser) with less than 5 mW of output power. The same room, 1-m tangent screen, and lighting conditions (lights on) were used for CVF and LVF testing. The examiner stood beside the patient (outside the patient’s field of view), seated 1 m from the tangent screen (Fig. 1). The laser was calibrated each time with a spot drawn on the wall measuring 1.75 mm diameter (visual angle 0.1°). Occluding one eye, the patient fixated on the tangent screen central button and verbally signaled when the laser target was noted. Initially, the laser target was presented in the periphery and was brought slowly toward fixation to assess for constriction in the four quadrants. Static points were tested in random fashion on either side of the vertical and horizontal meridians, near central fixation, around the blind spot, and in each quadrant (Fig. 2). The blind spot was repeatedly tested to assess fixation losses. Scotomas were recorded and rechecked for reproducibility.

Automated perimetry was performed prior to application tonometry using a Humphrey Visual Field Analyzer (Humphrey Instruments, San Leandro, CA) with standard testing conditions: 31.5 asb white background, a size III white stimulus, and either 24-2 FastPac or 24-2 SITA Standard protocol. Eyes with more than 33% fixation losses, false negatives, or false positive values were excluded for unreliable visual field parameters, as in current glaucoma trials.

Statistical analyses were performed using SAS 8.0 (SAS Institute, Inc., Cary, NC) and Stata 7.0 (StataCorp, College Station, TX). Sensitivities and specificities for LVF and CVF were compared using alternating logistic regression options for GEE estimation, adjusting for inter-eye and inter-test correlations.

RESULTS

One hundred seventy-five eyes of 90 patients were evaluated. Twenty-five eyes were excluded because of unreliable HVF parameters (including both eyes of 6 patients); 150 eyes of 84 patients were included in the final analysis. Twenty-five eyes underwent SITA threshold testing and 125 eyes had the FastPac program. No patient was excluded for fixation losses during LVF. There were 82 men and 2 women (approximating the Philadelphia VA Medical Center patient population). The mean age was 66 ± 12 years. Diagnoses included glaucoma (n = 63, 42%), glaucoma suspect (n = 72, 48%), anterior ischemic optic neuropathy (n = 5, 3%), hydroxychloroquine screening (n = 5, 3%), stroke (n = 3, 2%), and optic neuritis (n = 2, 1%).

HVFs were categorized by expert opinion as normal in 91 eyes (61%) and abnormal in 59 (39%). LVF was abnormal in 59 eyes (39%), while CVF was abnormal in 19 (13%) (Table 1A). The sensitivity of LVF, 73%, was significantly greater than that of CVF, 31% (P = 0.001, adjusted by inter-eye, inter-test correlation) (Table 1B). Sensitivities were 40% for LVF vs 10% for CVF with minimal HVF defects (n = 20), 91% for LVF vs 33% for CVF with moderate HVF defects (n = 33), and 83% for LVF vs 83% for CVF with severe HVF defects (n = 6). Average testing times were 0.5 minutes for CVF, 1.5 minutes for LVF, and 8.0 minutes for HVF.
For the eight ONTT field defect categories, the overall agreement between LVF and HVF was 60% (Table 2). Eight of the 25 excluded eyes had abnormal CVF and each had an abnormal LVF as well. Four other excluded eyes had abnormal LVF with normal CVF.

**DISCUSSION**

Confrontation techniques are widely used to screen for visual field defects as part of the neuro-ophthalmologic examination. Defects may be asymptomatic, particularly when they spare central vision, and may be difficult to identify by CVF techniques unless they are of moderate to severe density.1–3 Ideally, screening tests should be highly sensitive and specific, but a trade-off is usually required. If the subsequent diagnostic evaluation involves a test with minimal cost or risk, such as HVF, then screening should have high sensitivity.9

We have demonstrated that LVF can be used in the clinical setting with significantly greater sensitivity than confrontation as a screening tool. This LVF sensitivity increases if the field defects are of moderate density (−6.01 dB < MD < −20.0 dB). Intuitively, testing more spots could increase sensitivity, but time of testing would increase. Adding colored objects to confrontation could increase its sensitivity, but time of testing would increase. We believe that the majority of patients examined as outpatients by ophthalmologists, neurologists, and neuro-ophthalmologists receive CVF based on finger counting alone. Thus, we chose not to include colored objects in our experimental CVF protocol.

Because we did not select patients according to particular diagnosis, but rather by prevalence, most of our patients had glaucoma or were glaucoma suspects (90%). Because visual field defects in neurologic disorders are typically denser,2 LVF and CVF may have had greater sensitivities in this population of patients. Further testing of this laser technique is warranted in a group of patients with other neuro-ophthalmic conditions. Nonetheless, glaucoma is a reasonable disorder to test because the field defects may be subtle and are frequently undetectable with confrontation. Notably, HVF, the gold standard for visual field defects used in this study and many others, was originally developed for the detection of glaucomatous visual field defects.

One limitation of this study is that LVF was performed immediately prior to CVF. Therefore, the examiner knew if the LVF was abnormal prior to performing CVF. This order of screening may falsely raise the sensitivity of CVF, perhaps biasing the difference in sensitivities toward the null. In spite of this, the difference in sensitivities was highly significant (P = 0.001), making it an even more compelling observation. On the other hand, the observer could have been biased in the opposite direction by believing that

**TABLE 1A. Numbers of patients with normal and abnormal laser visual field (LVF) results and confrontation visual field (CVF) results for a given Humphrey visual field (HVF) result**

<table>
<thead>
<tr>
<th>LVF</th>
<th>Normal</th>
<th>Abnormal</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>71</td>
<td>20</td>
<td>91</td>
</tr>
<tr>
<td>Abnormal</td>
<td>9</td>
<td>50</td>
<td>59</td>
</tr>
<tr>
<td>Total</td>
<td>80</td>
<td>70</td>
<td>150</td>
</tr>
</tbody>
</table>

**TABLE 1B. Sensitivity and specificity of laser visual field (LVF) and confrontation visual field (CVF) testing to defects found with the Humphrey visual field analyzer**

<table>
<thead>
<tr>
<th>Field interpretation</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>95% CI*</td>
</tr>
<tr>
<td>LVF</td>
<td>0.73</td>
<td>0.59–0.81</td>
</tr>
<tr>
<td>CVF</td>
<td>0.31</td>
<td>0.17–0.38</td>
</tr>
</tbody>
</table>

* 95% Confidence interval adjusted by intereye, intertest correlation.

**TABLE 2. Graders’ interpretations of Humphrey visual field (HVF) and laser visual field (LVF)**

<table>
<thead>
<tr>
<th>Field interpretation</th>
<th>No. of eyes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>91 (61%)</td>
</tr>
<tr>
<td>Arcuate scotoma</td>
<td>21 (14%)</td>
</tr>
<tr>
<td>Double arcuate</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Altitudinal</td>
<td>12 (8%)</td>
</tr>
<tr>
<td>Enlarged blind spot</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Central scotoma</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Peripheral rim</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>Nasal step</td>
<td>15 (10%)</td>
</tr>
</tbody>
</table>
the laser was a superior detecting instrument. We tried to limit this bias by accepting any wrong answer as an abnormal CVF. Another limitation is that the sample population is predominantly male. There is no evidence, however, that females would perform any differently on visual field testing. Finally, LVF used only one size and one luminance (suprathreshold to any HVF stimulus). Varying the size and intensity of light could have raised the sensitivity of LVF. As recognized above, this would increase testing time.

In clinical practice, a black felt tangent screen can be placed on the wall behind the examining table or chair. To perform LVF, the patient can face the screen, and the pocket laser pointer can be quickly used to screen the visual field. A bedside consultation without the benefit of a tangent screen could be performed on a wall or ceiling with a central fixation target. This would provide a unique opportunity to screen patients who are unable to leave their hospital room for formal perimetry. Finally, outpatients who are unable to fit into or remain in a Humphrey perimeter would benefit from the increased sensitivity of LVF over CVF testing.

In this prospective study, we have demonstrated that LVF testing, performed using a commercially available laser pointer projected onto a tangent screen, is significantly more sensitive than confrontation visual field testing with fingers in screening for HVF visual field defects in this cohort. Although HVF and other perimetric techniques remain the standard for documenting visual field defects in patients with suspected afferent visual pathway disease, LVF may represent a more practical yet adequately sensitive method for office and bedside visual field screening.

REFERENCES
Posner-Schlossman Syndrome and Nonarteritic Anterior Ischemic Optic Neuropathy

Inci Irak, MD, Bradley J. Katz, MD, PhD, Norm A. Zabriskie, MD, and Paul L. Zimmerman, MD

Abstract: A 41-year-old woman with acute OD pain and decreased visual acuity presented with anterior uveitis, an intraocular pressure of 56 mm Hg, an open angle, ipsilateral nerve fiber bundle visual field defects, and optic nerve edema. With control of intraocular pressure and uveitis, visual acuity improved to 20/25, visual field defects persisted, and optic disc pallor developed. She has remained stable over 23 months of follow-up. This case represents a concurrence of glaucomatocyclitic crisis (Posner-Schlossman syndrome, PSS) and nonarteritic ischemic optic neuropathy (NAION). Although this combination occurs rarely, patients with PSS and other risk factors for NAION, including an optic disc that lacks a physiologic cup, should be protected against NAION by prophylactic treatment with ocular antihypertensive medications.


Posner-Schlossman syndrome (PSS), also known as glaucomatocyclitic crisis, is characterized by recurrent attacks of anterior nongranulomatous uveitis and elevated intraocular pressure (IOP). It is generally considered a benign, self-limited disease, and short-term use of corticosteroids and antiglaucoma medications controls the attacks. In a recent series of PSS cases, Jap et al found that 14 (26.4%) of 53 eyes had glaucomatous optic nerve damage. We report another complication of PSS, nonarteritic anterior ischemic optic neuropathy (NAION).

CASE REPORT

A 41-year-old Hispanic woman presented with a 4-day history of mild redness, pain, and blurred vision of the OD. She reported that a similar episode had occurred 3 months earlier and had improved with eyedrops prescribed at another institution. Her past medical history was significant for hypercholesterolemia and hypertension. She was using no systemic medications.

Visual acuity was 20/50 OD and 20/20 OS. There was a small relative afferent pupillary defect OD. Color vision was normal. She had some fine, round keratic precipitates and trace anterior chamber cell OD. Intraocular pressure was 56 mm Hg OD and 18 mm Hg OS by applanation. On gonioscopy, the ciliary body band was visible for 360 degrees OU without peripheral anterior synechiae or inflammatory deposits. Dilated funduscopic examination showed optic disc edema and flame hemorrhages on the disc margin OD and a normal appearing disc with no cup OS (Fig. 1). The patient was immediately treated with acetazolamide 500 mg BID PO, timolol 0.5% BID OD, latanoprost 0.005% QHS OD, and prednisolone acetate 1% QID OD.

On the following day, visual acuity was 20/50 and IOP was 13 mm Hg OD. Automated perimetry revealed dense superior and inferior arcuate defects OD and a full visual field OS (Fig. 2). One week later, visual acuity OD had improved to 20/25, the anterior chamber was quiet, and the IOP was 17 mm Hg. All medications were discontinued except latanoprost. Six months later, optic disc edema had been replaced by pallor (Fig. 3). Eleven months after presentation, the visual field defects persisted in the OD, while the field of the OS remained normal (Fig. 4). During 23 months of follow-up, there have been no further signs or symptoms of recurrent inflammation and IOP has been normal.

DISCUSSION

PSS is an uncommon, unilateral syndrome associated with recurrent anterior segment inflammation and elevated IOP. With acute attacks, the IOP is typically 40–60 mm Hg. Despite acute pressure elevations, patients complain only of mild discomfort and redness. After an attack, IOP and facility of aqueous outflow return to normal. The etiology of PSS is unknown, although herpes simplex virus has been isolated from aqueous humor of three patients during attacks, and there is an association with HLA-Bw54. Glaucomatous optic nerve damage is common after attacks.

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and many cases eventually evolve into a clinical picture similar to that of open angle glaucoma.\(^6\)

Whether elevated IOP contributes to NAION remains a controversial issue. Some authors have reported mildly elevated IOP in patients with NAION,\(^7\)\(^8\) while others contend that IOP is not significantly different in patients with NAION compared with controls.\(^9\) There are reports of NAION after IOP spikes associated with intracapsular cataract surgery,\(^10\) extracapsular cataract surgery,\(^11\) acute angle closure glaucoma,\(^12\) and herpes zoster ophthalmicus.\(^13\) It is interesting to note that the loss of vision often occurs some days after the acute elevation in IOP. It is possible that

FIGURE 1. One week after presentation, the right optic disc is diffusely swollen with flame-shaped hemorrhages. The left optic disc appears normal, although it has no physiologic cup.

FIGURE 2. One day after presentation, static threshold visual fields show dense superior and inferior nerve fiber bundle defects in the OD (mean deviation = -22.19 db) and no defects in the OS.
this delay occurs because acute ischemia leads first to axoplasmic flow stasis and optic nerve swelling. Swelling of the optic nerve head leads to further compromise of blood flow to the optic nerve, finally resulting in infarction. This mechanism has been proposed by Hayreh,\textsuperscript{14} who observed NAION preceded by optic nerve edema in four patients with bilateral, sequential NAION. Because the choroidal contribution to the circulation of the optic nerve is most susceptible to elevated IOP,\textsuperscript{15} Hayreh\textsuperscript{16} has also hypothesized that it is the balance between arterial pressure and IOP, both of which affect optic nerve perfusion, that is upset in cases of NAION. Although most cases of elevated IOP, including acute angle closure glaucoma, do not result in optic disc edema and irreversible vision loss,
variations in the vascular supply of the optic nerve head, along with other ocular and systemic risk factors, may predispose certain individuals to NAION during periods of elevated IOP.

Despite her young age, our patient had two risk factors for NAION: systemic hypertension and a small cup-to-disc ratio, or a "disk at risk". The temporal association between her acute rise in IOP and the precipitation of NAION leads us to conclude that elevated IOP in this case was likely the final insult that led to compromise of her optic nerve perfusion and subsequent NAION. Our case is similar to another recently reported case of NAION associated with PSS. In that case, a 71-year-old woman presented with acute vision loss, corneal edema, elevated IOP, and optic nerve edema. She went on to develop optic nerve pallor and a stable visual field defect.

Most ophthalmologists would agree that a patient with PSS and a large cup-to-disc ratio should be using ocular antihypertensive medications prophylactically because of the risk of glaucomatous damage. We recommend that ophthalmologists treating patients with PSS and other risk factors for NAION, especially a very small cup-to-disc ratio (absent physiologic cup, the "disk at risk") also consider treating these patients with ocular antihypertensive medications because of the fear that an attack of PSS might precipitate NAION.

REFERENCES
Solitary Intracranial Extra-osseous Plasmacytoma Presenting with Ophthalmic Signs

Suzanne O. Brannan, FRCOphth, Bethan N. Matthews, FRCOphth, Vijay Savant, FRCSEd, Ray D. Brown, FRCOphth, Timothy D. Matthews, FRCOphth

Abstract: Solitary plasmacytomas rarely develop in the skull, meninges, or brain. Ophthalmic signs as the initial manifestations of solitary intracranial plasmacytoma have rarely been described. We report the neuro-ophthalmologic, imaging, and pathologic findings for two patients. One patient presented with optic neuropathy, the second with bilateral sixth nerve palsies. Plasmacytoma is a treatable intracranial tumor that should be considered in the differential diagnosis of patients who present with optic neuropathy or sixth nerve palsy.


CASE REPORTS

Case 1
A 61-year-old woman with a history of Crohn’s disease and hemicolectomy presented with a 3-week history of painless deteriorating vision affecting the OS, and associated with persistent left frontal headache of several weeks’ duration. Best-corrected visual acuities were 20/20 OD and count fingers OS. There was a left afferent pupillary defect. Ocular motility examination was normal, as were slit-lamp biomicroscopy and funduscopy. Color vision, as assessed by Ishihara Pseudo-isochromatic Charts, was reduced in the OS. Constriction of the left nasal field was detected on Goldmann perimetry. The right visual field was full. Neurological examination elicited reduced sensation in the second division of the left fifth nerve.

Cranial computed tomography (CT) revealed a well-defined mass in the left cavernous sinus that extended anteriorly through the optic foramen to abut the inferior aspect of the left optic nerve (Fig. 1A). Magnetic resonance imaging (MRI) indicated a homogeneously enhancing mass at the apex of the orbit with possible involvement of the adjacent bone, including the left clinoid process, and extending into the orbit (Fig. 1B). These imaging features were interpreted as indicating a left para-sellar meningioma.

A left fronto-temporal craniotomy was performed for partial excision of the tumor. The portion encircling the left optic nerve was removed; the portion extending distally to the anterior limit of the cavernous was left behind. The patient made a good postoperative recovery, but the visual acuity OS fell to no light perception. Light microscopy of the tumor showed atypical plasma cells (Fig. 1C). Immunoperoxidase staining for immunoglobulin light chains confirmed kappa restriction, consistent with plasmacytoma (Fig. 1D). Myeloma screen included a negative marrow aspiration, skeletal survey, urine protein electrophoresis, and 24-hour urine for Bence-Jones protein. Serum protein electrophoresis demonstrated an abnormal monoclonal IgG kappa paraprotein band.

The patient underwent radiotherapy to the residual tumor over a period of 4 weeks (50 Gray units). A 1-year follow-up MRI revealed complete resolution of the tumor (Fig. 1E). Visual function was unchanged. The patient’s hematological indices were within normal limits.

Case 2
A 50-year-old man presented with sudden horizontal binocular diplopia. For the previous 8 weeks, he also had been complaining of constant headache that radiated from the left occiput to the fronto-parietal region. Apart from asthma, his past medical history was unremarkable. Best-corrected visual acuities were 20/20 OD, 20/30 OS. He could not abduct the OS beyond the midline. There was also a right abduction deficit, measuring approximately 50% of normal excursion. A diagnosis of bilateral sixth nerve palsy was made. No other abnormal neurologic signs were found, and his BP, blood sugar, and full blood counts were normal.

MRI showed extensive tumor within the clivus (Fig. 2A), bulging backwards and deforming the anterior aspect of the pre-pontine cistern (Fig. 2B). A diagnosis of bilateral sixth nerve palsy was made. No other abnormal neurologic signs were found, and his BP, blood sugar, and full blood counts were normal.

MRI showed extensive tumor within the clivus (Fig. 2A), bulging backwards and deforming the anterior aspect of the pre-pontine cistern (Fig. 2B). The petrous apex on both sides was eroded, more on the left. The differential
Intracranial Extra-osseus Plasmacytoma

FIG. 1. Case 1. A: Axial CT shows a well-defined mass in the left cavernous sinus with extension through the optic foramen and erosion of the anterior clinoid process. B: Axial T_1 enhanced MRI shows a homogeneously enhancing mass at the apex of the orbit with extension into the orbit. C: Hematoxylin-eosin stain of biopsy demonstrates atypical plasma cells. D: Immunoperoxidase stain for light chains confirms kappa restriction (dark-staining cells). E: Axial T_1 enhanced MRI one year after surgery and chemotherapy shows resolution of the mass.

The diagnosis included metastasis, chordoma, plasmacytoma, or nasopharyngeal carcinoma.

A transnasal biopsy of the mass showed atypical plasma cells, including a few binucleate forms. Immunohistochemical reactions indicated that this was a plasmacytoma or an intracranial manifestation of multiple myeloma with kappa light chain monoclonality. A skeletal survey, bone marrow aspirate, serum electrophoresis, 24-hour urine collection for Bence-Jones protein, and all hematological parameters were normal.

He was treated with dexamethasone 4mg/d and subsequently underwent fractionated radiotherapy (45 Gray in
FIG. 2. Case 2. A: Axial T2 MRI shows an extensive homogeneous mass in the clivus. B: Sagittal T1 MRI shows the mass extending into and deforming the anterior aspect of the pre-pontine cistern.

25 fractions), followed by CVAMP chemotherapy for 4 months. The sixth nerve palsies failed to resolve, so he underwent botulinum toxin injections into both medial recti, which allowed him to maintain binocular single vision with a slight head posture.

Eight months later, he remained free of systemic symptoms. Follow-up neuroimaging has not been requested because of the known radiosensitivity of these tumors and the patient’s stable clinical status.

DISCUSSION

Most cases of solitary extraosseous plasmacytoma occur in the nasopharynx, upper respiratory tract, lamina propria of the gastrointestinal tract, or other soft-tissue areas (1). Intracranial plasmacytomas are rare (2). A review of the literature by Spaar (3) uncovered 32 cases up to 1980. In half of these cases, there was evidence of systemic disease, whereas in the others the plasmacytoma was a solitary disorder.

Patients with a solitary plasmacytoma often have a more favorable course than those with systemic myeloma. Therefore, determining whether a plasmacytoma is solitary is important prognostically. A study of 114 patients with solitary plasmacytoma (4) found that approximately 70% were alive after 10 years. In their case series, Bindal et al. (5) found that, in patients with intracranial plasmacytoma, multiple myeloma is unlikely to develop during the long term if it is not evident in the early postoperative period. The prognosis of solitary plasmacytoma is further altered by its location. Most patients with extraosseous plasmacytoma, which commonly involves the head and neck region, may be curable because the tumor is radiosensitive (6).

Included in the differential diagnosis of plasmacytoma, based on morphologic criteria, is plasma cell granuloma. The demonstration of immunoglobulin monoclonality confirms a diagnosis of a neoplasm and excludes a diagnosis of granuloma, in which the immunofluorescent study would reveal a polyclonal population of plasma cells producing all three major classes of immunoglobulins.

Clarke (7) classified cranial myelomas into three clinical groups: 1) Group 1, consisting of tumors that involve the skull base but that do not involve brain parenchyma; they characteristically cause cranial nerve palsies; 2) Group 2, consisting of tumors that involve brain parenchyma, with or without origin in the skull; and 3) Group 3, consisting of intra-orbital tumors.

Our Case 1 belongs in Clarke’s Group 2, demonstrating a clinical picture of an intracranial tumor syndrome without bone or convexity dura mater involvement. The rarest type of intracranial plasmacytoma, it presents with multiple neurologic symptoms and signs, occasionally with those of a space-occupying lesion and raised intracranial pressure. An optic neuropathy usually would be associated with other neurologic signs (1). Isolated optic nerve compression from an intracranial plasmacytoma has been reported only rarely (8–10). In two cases, a initial diagnosis of retrobulbar neuritis was made and the patients demonstrated transient alleviation of symptoms with systemic corticosteroid therapy. To our knowledge, our Case 1 is the first reported example of a solitary intracranial extra-osseous plasmacytoma involving the cavernous sinus and the optic nerve.
Our Case 2 belongs in Clarke's Group 1, presenting with bilateral sixth nerve palsies associated with a lesion at the base of the skull. The sixth nerve is the most common cranial nerve affected by multiple myeloma, either in isolation or combination with other cranial neuropathies (7,11).

Our Case 1 emphasizes the potential for plasmacytoma to mimic meningioma on neuroimaging. Our Case 2 emphasizes how the elicitation of a subtle contralateral abduction deficit in a patient with an apparently unilateral abduction deficit changed the diagnostic focus.

REFERENCES
Siegrist Streaks in Giant Cell Arteritis

Dustin J. Coupal, MD, and Anil D. Patel, MD, FRCSC, FACS

Abstract: A patient who presented with symptoms of giant cell arteritis was found to have a right ophthalmic artery occlusion. One month after initial evaluation, the peripheral retina demonstrated multiple linear bands of chorioretinal atrophy known as Siegrist streaks. Although most commonly described in the setting of acute hypertension, Siegrist streaks also occur in patients with giant cell arteritis.


A 78-year-old woman was referred for urgent neuro-ophthalmic evaluation with a 4-day history of transient visual obscurations in the OD followed by sudden vision loss in that eye. She described a 6-week history of severe headaches, jaw claudication, scalp tenderness, fatigue, and unintentional weight loss.

Examination revealed a visual acuity of no light perception in the OD and 20/30 in the OS. External examination revealed bilateral ulcerated scalp lesions consistent with giant cell arteritis.
Siegrist Streaks in Giant Cell Arteritis


with scalp necrosis. Pupillary examination showed a large right afferent pupillary defect. The visual field in the OS was full. The intraocular pressures were within normal limits. Ophthalmoscopy revealed pallid swelling of the optic disc and cloudy swelling of the retina, findings consistent with a right ophthalmic artery occlusion (Fig. 1A). The OS was unremarkable.

Results of blood work revealed a Westergren erythrocyte sedimentation rate of 26mm/h and an elevated C-reactive protein of 29mg/l (normal = 0–8mg/l). The patient was tentatively diagnosed with giant cell arteritis (GCA) and was admitted to the hospital for intravenous corticosteroid therapy. A temporal artery biopsy confirmed the clinical suspicion of GCA.

Reevaluation 1 month later showed marked right optic disc pallor and significant sclerosis of all branches of the right central retinal artery (Fig. 1B). Identified within the mid-peripheral retina were a number of linear and wedge-shaped retinal lesions that are known as Siegrist streaks (Fig. 1C). Fluorescein angiography vividly demonstrated well-defined radiating bands of retinal atrophy (Fig. 1D).

Siegrist streaks initially were identified and documented in 1899 by Siegrist (1), who had recognized a peculiar pattern of pigmented retinal lesions in two patients, one with GCA and the other with malignant hypertension. Since that time, other reports of Siegrist streaks have been published, most often in patients with severe arterial hypertension and more rarely in patients having GCA (2–4). Hayreh (5) reported that in 123 eyes with ocular involvement in GCA, 10 eyes were found to have chorioretinal ischemic lesions, which we believe are Siegrist streaks.

Siegrist streaks develop as a late result of non-perfusion of choroidal vessels causing severe outer retinal ischemia (2,4). McLeod has suggested that outer retinal infarcts occur more frequently in patients with GCA when there is combined involvement of the central retinal and posterior ciliary circulations (6). Histopathologically, Siegrist streaks have been shown to consist of sclerosed choroidal vessels with overlying obliteration of the choriocapillaris and secondary retinal pigment epithelial atrophy (7). A reactive retinal pigment epithelial hypertrophy and hyperplasia occurs along the margins of the streaks 2 or 3 weeks after the onset of chorioidal ischemia (5).

Related to Siegrist streaks are similar manifestations of impaired choroidal perfusion known as Elschnig spots. These spots are small isolated circular areas having central retinal pigment, epithelial pigment clumping, and a surrounding halo of depigmentation (8). Whereas Siegrist streaks tend to occur along the course of sclerosed choroidal vessels, Elschnig spots occur in isolation secondary to focal obliteration of the choriocapillaris. Siegrist streaks and Elschnig spots may be found together in the same patient or may occur separately.

The significance of Siegrist streaks in patients diagnosed with GCA is not well documented, but when found in the setting of acute hypertension, they are considered to reflect a relatively poor general health prognosis (2,3).

References


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Retinal Vascular Abnormalities in Neurofibromatosis Type 1

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Abstract: Microvascular retinal abnormalities, presenting in a corkscrew configuration, have been very recently described in patients with neurofibromatosis type 1 (NF-1). We report one more patient with NF-1 who had distinctive corkscrew retinal vessels superior and inferior to the fovea. This patient further supports the existence of a true association between this recently described retinal finding and NF-1.


A 31-year-old Greek man was referred for a routine ophthalmic examination. He had been diagnosed with neurofibromatosis type 1 (NF-1) according to the criteria established by the National Institutes of Health (1). Best-corrected visual acuity was 20/20 bilaterally. Anterior segment examination revealed multiple Lisch nodules bilaterally. Retinal examination of the OD was unremarkable. Retinal examination of the OS revealed tortuous retinal venules in a corkscrew configuration superior to the fovea, adjacent to which a microvascular collateral-like network was noted. Inferior to the fovea, similar but less prominent tortuous venules were seen (Figs. 1 and 2). No retinal edema was present clinically. The patient refused to undergo fluorescein angiography.

NF-1 is a common genetic disorder resulting in the formation of a variety of benign and malignant tumors (2). It has an autosomal dominant mode of inheritance with 100% penetrance and variable expressivity. The responsible gene has been located on the long arm of chromosome 17 and encodes for a protein termed "neurofibromin," which appears to be a tumor-suppression protein.

FIG. 1. Fundus, OS, shows microvascular abnormalities superior and inferior to the fovea.
Findings in the fundus include choroidal hamartomas (present in one-third to one-half of adults with NF-1), retinal astrocytic hamartomas, combined retinal and retinal pigment epithelial hamartomas, and retinal capillary hemangiomas (3).

In 2002, Muci-Mendoza et al. (4) described a novel retinal finding in NF-1, distinctive microvascular abnormalities noted in 12 out of 32 (37.5%) patients. In 10 cases, the anomaly was very subtle, involving a second or third order venule, a tributary of the superior or inferior temporal veins, or, less frequently, the nasal veins. The tortuous vessel had a corkscrew appearance and ended in a minute tuft. In two of the patients, however, more striking abnormalities were observed: a venovenous anastomosis in the nasal retina and an extensive arteriovenous malformation coexisting with an epiretinal membrane. Two of these 12 patients also had choroidal neurofibromas. Fluorescein angiography obtained in half of the cases did not reveal any leakage. The condition did not disturb vision. According to the authors, this finding is a new retinal marker for NF-1.

**References**


Rocky Mountain Spotted Fever as a Cause of Macular Star Figure

Michael S. Vaphiades, DO

Abstract: An 86-year-old woman with a history of tick bites in the previous months developed subnormal visual acuity in both eyes, keratic precipitates, anterior chamber and vitreous cells, optic disc edema, retinal hemorrhages, and retinal arteriolar sheathing. She had no fever or skin rash. Three weeks later, binocular macular star figures appeared. Brain imaging was negative; cerebrospinal fluid disclosed a lymphocytic pleocytosis and elevated protein. The serum *Rickettsia rickettsii* antibody test was markedly positive, establishing a diagnosis of Rocky Mountain Spotted Fever (RMSF) as the cause of the ophthalmic findings. Despite treatment with oral doxycycline, these findings improved only modestly. Although neuroretinitis has been previously described in RMSF, macular star has not been documented.

Case
An 86-year-old woman noted visual loss in both eyes for 1 month. She had several tick bites over the previous 6 months and had no constitutional symptoms, fever, or skin rash. Medical history included bilateral hearing loss for greater than 20 years and exposure to tuberculosis (TB).
30 years previously with a history of positive TB skin tests since.

Examination showed a normal blood pressure and heart rate. Best-corrected visual acuity was 20/30 in the OD, 20/200 in the OS, with normal color vision. Pupils were pharmacologically dilated from a previous examination. She had normal intraocular pressures, keratic precipitates, and anterior chamber and vitreous cells binocularly. She had optic nerve edema in both eyes with retinal artery sheathing in the OD and flame-shaped hemorrhages in the OS (Fig. 1).

Cranial and orbital magnetic resonance imaging showed only periventricular white matter changes, considered normal for age. Complete blood count, electrolytes, glucose, syphilis testing, antinuclear antibodies, erythrocyte sedimentation rate, angiotensin converting enzyme, serum protein electrophoresis, anti-neutrophilic cytoplasmic antibody, and chest x-ray were normal. Tuberculosis skin test was positive at 13 mm (previous exposure). A lumbar puncture showed an opening pressure of 13 cm water, white blood cells 58/mm$^3$ (100% monocytes), red blood cells 26/mm$^3$, glucose 69 mg/dl, protein 109 mg/dl (normal less than 60 mg/dl), and normal Venereal Disease Research Laboratory (VDRL) test, cryptococcal antigen, gram stain and fungal cultures, cytology, and vitreous biopsy.

Three weeks later, the visual acuity had fallen to 20/40 OD and count fingers OS, with a 1.2 log relative afferent pupillary defect in the OS. Ophthalmoscopy now showed a partial macular star figure in the OD and a complete star figure in the OS (Fig. 2). Goldmann visual fields showed constriction binocularly (Fig. 3). Bartonella henselae, Borrelia burgdorfi, Toxoplasma gondii, and Ehrlichia chaffeensis tests were all normal. A serum Rickettsia rickettsii antibody test showed an IgG of 2.6 IV (normal = 0-0.9 IV) and IgM of 1.5 IV (normal = 0-0.9 IV). Oral doxycycline 100 mg BID for 14 days was prescribed. Follow-up examination 3 weeks later showed improvement of the optic nerve edema binocularly with a visual acuity remaining at 20/40 in the OD and improved to 20/100 in the OS. The macular star figures persisted.

This patient developed Leber's stellate neuroretinitis caused by RMSF without the fever and rash usually associated with this disease. There are only nine cases of neuroretinitis from RMSF reported in the literature (1-4). Unlike this case, all other cases had associated constitutional symptoms and none had a macular star figure (1-4).

Hudson et al. (5) reported two patients with retinal findings from the related infection murine typhus (Rickettsia typhi) and noted a similarity to cat-scratch disease. This implied the presence of a macular star, but none was documented in their cases (5). Other reported ophthalmic signs of RMSF are keratic precipitates, ulcerative keratitis, conjunctivitis, uveitis, Roth spots, papilledema, and third and sixth cranial nerve palsies (1-4,6).

RMSF was first recognized by Major Marshall Wood in 1896 (7). Ten years later, Ricketts demonstrated tick transmission of the organism that would eventually bear his name, Rickettsia rickettsii (7), an obligate intracellular gram-negative coccobacillus for which ticks serve as vectors and reservoirs. The organism is usually harbored by the wood tick (Dermacentor andersoni) and dog tick (Dermacentor variabilis) (7,8). Only 56% of patients remember dog or tick contact (9). The disease is endemic in the southeastern United States but has been reported in 46 states (10). RMSF is the most frequent cause of fatality of tick-borne disease in the United States (7). Without therapy, the mortality rate may be as high as 80% (10). Unlike this patient, most afflicted patients experience fever greater than 102°F, headache, and a petechial rash on the palms of the hands and soles (7,8). Only 52–62% of patients experience the complete triad (9). Two-thirds of patients have cerebrospinal fluid abnormalities, including elevated protein levels and a mononuclear pleocytosis, as did my patient (9). Pulmonary edema and symptoms of an acute abdomen may also develop (8). Neurologic symptoms include aphasia, hemiparesis, deafness, confusion, and encephalitis (11), none of which were present in my patient.

FIG. 3. Goldmann perimetry shows constricted visual fields in both eyes.

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Treatment consists of oral doxycycline (7,8). Of the nine cases of RMSF-associated neuroretinitis, doxycycline improved the constitutional symptoms and uveitis in one patient, but there was no change on the fundoscopic examination (4). In another patient treated with intravenous chloramphenicol, there was near complete resolution of the retinopathy (3); in one patient treated with neomycin, the clinical course progressively improved without specific mention of the retinal findings (1). In the other six cases of reported RMSF with neuroretinitis, there was no mention of clinical outcome (2).

References
The Multifocal Visual Evoked Potential

Donald C. Hood, Ph.D., Jeffrey G. Odel, M.D., Bryan J. Winn, B.A.

Abstract: With the multifocal technique, visual evoked potentials (VEPs) can be recorded simultaneously from many regions of the visual field. For the multifocal VEP (mfVEP), the patient views a display that typically contains 60 sectors, each with a checkerboard pattern. The display covers about the same retinal area as the 24-2 Humphrey visual field (HVF). However, due to the scaling of the sectors of the mfVEP display, the fields are sampled differently by the mfVEP and HVF. To assess local defects in the visual field, the mfVEP responses must be compared with normal controls. These comparisons require relatively sophisticated analyses and software. Whereas the mfVEP can be recorded relatively easily with the same equipment used to record multifocal electroretinograms (mfERGs), the software needed to perform the analysis is not yet widely available. The mfVEP is valuable for ruling out non-organic visual loss, diagnosing and following patients with optic neuritis/multiple sclerosis, evaluating patients with unreliable or questionable HVFs, and following disease progression. When combined with the mfERG, diseases of the outer retina (before the retinal ganglion cells) can be distinguished from diseases of the ganglion cells and/or optic nerve. The difficulties encountered in recording and analyzing mfVEP responses are greater than those involved in full-field VEP testing. Thus, in its current form, the mfVEP is best recorded and interpreted by ophthalmologists and electrophysiologists experienced with the technique. However, this technique is developing rapidly; advances in commercial hardware and software are expected in the near future.

What is the Multifocal Visual Evoked Potential (mfVEP)?

The visual evoked potential (VEP) is not new to neuro-ophthalmology. Thirty years ago, Halliday et al. (1,2) reported delayed VEP responses in patients with optic neuritis/multiple sclerosis (ON/MS). Although some neuro-ophthalmologists still obtain a conventional VEP to help in the diagnosis of ON/MS or to rule out non-organic (psychogenic) visual loss, others find little or no use for this technique. The limited use of the VEP can be traced, at least in part, to the size of the stimuli used. The pattern reversal VEP is recorded to a display of at least 15° in diameter (3). Thus, local defects can easily be missed. The bright flash VEP uses full-field illumination and elicits a mass response from the anterior visual pathway. Thus, responses from abnormal regions of the field are summed with those from normal regions. Further, the pattern reversal VEP is dominated by responses from the lower field in most individuals (4-8). Thus, large defects in the upper field can be missed with the conventional VEP (8,9). In general, the lack of spatial information limits the usefulness of the technique.

The multifocal VEP (mfVEP), based on Sutter's multifocal electroretinogram (mfERG) technique (10), was developed by Baseler, Sutter et al. (11) to provide local VEP responses from the visual field. As described below, the technique combines conventional VEP recording techniques with a display that is subdivided into a number of regions, each of which has an independent stimulus controlled by specialized software. From a single, continuous EEG signal, a sophisticated mathematical algorithm extracts the VEP response generated by each of the independent regions. As typically used today, multiple individual VEP responses are generated simultaneously from 60 or so regions of the central 20 to 25° radius of the visual field.

Baseler et al. (11) suggested that the clinical utility of the mfVEP is limited because of the great variation of responses obtained from identical locations in normal individuals. Later, Graham et al. (12) and Hood et al. (13-15) improved the clinical utility of the mfVEP by introducing interocular comparisons to the analysis, as mfVEPs elicited from the right and left eyes of normal individuals are virtually identical. More recently, it has been demonstrated that a strictly monocular test, if properly analyzed, could have clinical utility as well (16-18). Thus the mfVEP is starting to find its role in the clinic, especially in the management of glaucoma (18).

The same equipment used to record mfERGs can record mfVEPs, and hundreds of centers have this equipment. However, only a handful of centers around the world are...
routinely recording mfVEPs. While the mfVEP can be recorded relatively easily with existing equipment, the software needed to identify local defects is not yet widely available. At the moment, we know of only two groups that have published these techniques, our group (13,17–19) and Graham, Klistorner et al. (12,16,20). However, the mfVEP technique is developing rapidly and advances in commercial hardware and software are expected in the near future.

**HOW ARE mfVEP RESPONSES OBTAINED?**

**The Equipment**

The mfVEP can be recorded with the same equipment available for mfERG recordings. Although the equipment and VERIS software developed by Sutter (Electro-Diagnostic Imaging (EDI), San Mateo, CA) dominate the market, equipment from other companies (such as Roland Instruments, Germany) can be found outside the United States. Recently, an Australian company has developed a system strictly for recording mfVEPs. This AccuMap system (ObjectiVision Pty, Ltd., Sydney, Australia) is based on the work of Graham, Klistorner et al. (12,16,20). At this time, its availability in the United States is uncertain. Further, this is an evolving technology and developments in hardware and software are certain to appear soon. For example, EDI plans to enhance its analysis of the mfVEP.

**The Display**

Figure 1A shows the mfVEP display used in the work summarized here. Similar to the one originally described by Baseler et al. (11), it is a standard part of the VERIS software developed by Sutter (10). The Roland and AccuMap systems use a modification of this display. There are 60 sectors, each containing 16 checks—8 black and 8 white. The sectors and the checks are scaled, based on cortical magnification, to be of approximately equal effectiveness for cortical stimulation (11). For example, the central most sectors are about 1° wide, whereas the outermost sectors exceed 7°.

**Recording the Signal**

In general, the VEP signal is recorded with the same electrodes and amplifiers used for conventional VEP recording. The critical differences are in the display, the method of stimulation, and the analysis of the raw records. For the records shown here, a single continuous VEP (EEG) record is obtained with an active electrode placed 4 cm above the inion, a reference electrode placed at the inion, and a ground electrode placed on the forehead. In addition, we record additional channels of VEP activity by placing two active electrodes 1 cm above and 4 cm lateral to the inion (17–19). This method, suggested by Klistorner and Graham (20), yields better responses in some parts of the field, especially along the lower midline (16–18,20). By analyzing the records offline with programs written in MATLAB, the information from the different electrodes can be combined (17–19). In the case of the AccuMap system, the software is built into the system. Technical details can be found elsewhere (16–21).

From a single, continuous VEP (EEG) signal, the software extracts 60 mfVEP responses, each associated with one of the sectors of the display. This is the “magic” of the multifocal technique: 60 responses are obtained from one record. To get a sense of how this magic is produced, the nature of the local stimulation of each sector must be examined.

**Extracting the Local Responses from the Signal**

To understand the mfVEP technique, it is essential to understand how each of the sectors is varied during the test. Each sector is an independent stimulus. Every 13.3 msec, the frame of the monitor changes and each sector has a 50% chance of reversing contrast or staying the same. Figure 1B shows a series of frame changes in which either the contrast is reversed or no change takes place. Each of the 60 sectors of the display in Figure 1A goes through its own pseudo-random sequence. In fact, the 60 pseudo-random sequences are the same series of “reversals” or “no change”, but each of the sectors starts its sequence at a different point in the series. The reason for this, and the nature of the pseudo-random series, are technical details that the reader does not need to understand in depth. It is sufficient to know that these pseudo-random sequences allow the software to rapidly extract the response associated with each of the 60 sectors (10). [Readers interested in learning more about the technical details should consult references 10 and 21.]

How does the software extract 60 responses from a single record? Technically, each response is the result of a serial correlation between the stimulation sequence of a particular sector and the single continuous response. Figure 1C provides a non-technical explanation. If one summed the first 200 msec of all of the records following the point in time at which a particular sector reversed in contrast, the result would look like the response R in Figure 1C. Likewise, if one summed the first 200 msec of all of the records following the point in time at which the same sector did not reverse in contrast, the result would look like NR in Figure 1C. Response R should contain the responses to all the sectors that reversed including the sector in question. NR, on the other hand, will have the responses to all sectors except the sector in question. The difference between R and NR is the response to the sector in question. Whereas the software could calculate the 60 mfVEP responses this way, it does not. The pseudo-random sequence, described above, is chosen in a certain way (an m-sequence) such that, when coupled with a special algorithm, the software can make these calculations very quickly (10). Because of the patent
FIGURE 1. The multifocal visual evoked potential (mfVEP) technique. A. The display. There are 60 scaled sectors. B. The stimulation. A series of frame changes for a sector of the mfVEP. C. The response extraction. D. The signal and noise windows used for quantitative analysis. The sum of the responses to the sectors in the upper and lower fields for 14 normal individuals. C1 and C2 are the initial negative and positive components of the mfVEP. Dashed lines indicate the 'signal window' (45 to 150 ms) from which the amplitude of the response is taken and the ‘noise window’ (325 to 430 ms) used in the analysis. The summed responses from the upper and lower field are reversed in polarity.
held by EDI on the m-sequence technique, other manufactures (including Roland and ObjectiVision) of multifocal equipment use different methods for extracting the multifocal responses.

Displaying the Responses

Figure 2A shows the 60 mfVEP responses for monocular stimulation of the right (blue) and left (red) eyes from a normal subject. Note that these responses are positioned so that they do not overlap. Thus the scaling is arbitrary, as the circles in color indicate. For example, there are 12 responses in the central 2.6° (5.2° in diameter), while each of the responses in the outer ring is produced by regions that are larger than the entire central 2.6°.

NORMATIVE VALUES AND REPEAT RELIABILITY

Although mfVEPs have been recorded from normal controls (12,13,16,17), these results are not reported in a way that would be of use to other investigators. Further, the currently available versions of the VERIS and Roland software do not have normative values for the mfVEP; the AccuMap system will have them. Even so, for all electrophysiological tests, it is important that each clinic establish its own age-related normative values. This is particularly true for the mfVEP, where the ability to detect subtle defects will depend upon the level of noise, which can vary from one setting to another.

The ability to track the progression of a disease will depend on various factors, but it is clear that good repeat reliability is essential. Relatively little has been published on repeat reliability, although the existing evidence suggests it is very good (11,12,22). In a recent study of 15 control subjects and 10 patients with glaucoma, the repeat reliability of the mfVEP was better than that of the HVF (22).

RELATION TO CONVENTIONAL VEP

The mfVEP response bears a superficial resemblance to the conventional pattern-reversal VEP. Figure 1D contains the sum of all the responses to the sectors in the upper and lower fields of 14 normal individuals. [Note that these responses are shown reversed in polarity as compared with the way they are displayed in the VERIS software because the software reverses the polarity (7,18,21).] In the responses from the lower field, there is an initial negative component (C1) around 65 ms followed by a prominent positive component (C2) around 95 msec, analogous to the N75 and P100 of the conventional pattern reversal VEP (3). In a study designed to compare the conventional VEP and mfVEP under similar conditions, Fortune and Hood (7)
concluded that the local mfVEP response is not simply a "little conventional VEP." The C2 component of the mfVEP is smaller and slightly faster than the P100 of the conventional VEP. Further, whereas the mfVEP from the upper visual field is reversed in polarity as compared with that of the lower field, the conventional VEP generally has the same polarity for upper and lower field stimulation. Fortune and Hood (7) concluded that these differences are due to the fast mfVEP sequence, which they speculate is producing a response with a smaller extrastriate contribution than that of the conventional VEP.

THE mfVEP PROBABILITY FIELD

To introduce our method for displaying the results of the mfVEP, consider the following case. Patient 1, a 43-year-old man, presented with a 4-week history of "blurry vision" in the superior temporal field of his OS. He was under stress at work and in the process of a divorce. Humphrey visual fields (HVF) OS showed abnormalities (Fig. 3A), but there were abnormal points in his HVF for the OD as well. Further, his HVF results were suspect because the number of fixation losses was high (13/15 OS and 7/14 OD) and the patient had alcohol on his breath while performing the test. Thus, he was referred for a mfVEP. His records are presented in Figure 2B.

In a number of locations, the mfVEPs from his OS (red traces in Fig. 2B) are clearly smaller than those from his OD (blue traces). The asterisks in Figure 2B indicate four examples. On the other hand, the plus symbols show two locations where the responses from the two eyes are nearly identical. To provide a quantitative measure of these differences, probability plots are derived for the mfVEP analogous to the probability plots for the HVF (Fig. 3A).

The first two panels in Figure 3B are probability plots for the mfVEPs of the left and right eyes compared with the mfVEPs from the left and right eyes of a group of control subjects. For each sector in the field, the amplitude of the mfVEP is determined for the response in a time window from 45 to 150 msec (see "signal window" in Fig. 1D). The amplitude of the response is compared with the mean and standard deviation of the mfVEP amplitudes of a group of control subjects. [Technically, the root-mean-square is taken as the measure of amplitude and the analyses are based on a comparison, the signal-to-noise ratio, of the response in the signal window to the response in the "noise window" (Fig. 1D) (17-19,23).] Each of the squares in the mfVEP probability plots in Figure 3B is located at the center of one of the sectors of the mfVEP display (Fig. 1A). A colored square indicates that the mfVEP was statistically significant at either the 5% (deshaturated color) or 1% (saturated color) level, while the color indicates whether it was the left (red) or right (blue) eye that was significantly smaller than normal.

In many patients, an interocular comparison of the mfVEPs is a more sensitive indicator of damage (18,24). In fact, in our experience, the interocular comparisons are
more valuable to the neuro-ophthalmologist than are the
monocular results. The interocular mfVEP probability plot
for this patient is shown as the rightmost panel of Figure 3B.
To obtain this plot, the ratio of the amplitudes of the mfVEP
of the two eyes is measured for each sector of the display
(13-15,18,24). This ratio is then compared with the ratios
from a group of controls to establish 5% and 1% signifi-
cance levels. The result is coded as in the case of the mon-
ocular fields. [See Hood and Greenstein (18) for a review of
the derivation and use of both monocular and interocular
probability plots, and Graham, Klistorner et al. (12,16,20)
for a similar approach.]

COMPARING mfVEP FIELDS WITH STATIC
VISUAL FIELDS

The results from the mfVEP can be directly compared
with those from the HVF. To make this comparison easy,
the HVF and mfVEP probability plots are presented on
the same scale in Figures 3 to 5. For example, the circles in
the leftmost panels of Figures 3A and 3B have radii of 2.6°
(red), 9.8° (blue) and 22.25° (green). To obtain an interocu-
lar HVF (15,18) (rightmost panel in Fig. 3A), the total de-
viation scores for the right eye are subtracted from that of
the left and coded as in the case of the mfVEP. The signifi-
cance levels are based on the sensitivities of a group of 100
normal individuals (25). Now the three HVF plots (Fig. 3A)
can be compared with the three mfVEP plots, two mono-
cular and one interocular (Fig. 3B).

In the case of this patient, the mfVEP is confirming a
defect in the OS on both the monocular and interocular
plots. However, the HVF and mfVEP are not in complete
agreement. For example, the HVFs from both eyes show
defects in the lower field and these are not seen in the
mfVEP plots. There are many reasons for a disagreement
between the mfVEP and HVF results (15). In this case, the
disagreement has a simple explanation. The patient was not
a good field taker and the HVFs were not reliable.

CLINICAL APPLICATIONS

Since October 1998, we have performed mfVEPs on
over 200 patients evaluated by two neuro-ophthalmolo-
gists, Drs. Myles Behrens and Jeffrey Odel. We summarize
our experience by grouping patients into the most common
reasons for seeking a mfVEP.

Ruling Out Non-Organic Visual Loss

Like the conventional VEP, the mfVEP can be used
to rule out non-organic visual loss. The mfVEP has the ad-

tantage in that it provides a topographical representation,
which can be compared with the patient’s visual fields. The
mfVEP in Patient 1, suspected of having non-organic visual
loss, clearly indicated an organic problem. The responses
from the OS are significantly depressed in a number of lo-
cations shown as the red squares in Figure 3B. The re-
dponses from four of these locations are labeled with the
asterisks in Figure 2B and shown in the inset in Figure 3B
(rightmost column). For comparison, the inset in Figure 3B
also shows two responses within the normal range (plus
symbol in Fig. 2B). As the abnormal region is relatively
small, it probably would have been missed by the conven-
tional VEP. In any case, the presence of a clearly abnormal
mfVEP in a region that corresponded to the patient’s sub-
jective complaint clearly indicated that this was an organic
problem. Blood tests revealed Leber hereditary optic neu-
ropathy. He subsequently lost vision in his other eye and
developed bilateral optic atrophy.

More typically, patients who are tested to rule out a
non-organic cause have normal mfVEPs. We have previ-
ously published an example of a patient with a dense infer-
ior bitemporal quadrantanopsia in whom the normal
mfVEP confirmed a non-organic diagnosis (26). In addi-
tion, the mfVEP can detect a non-organic overlay that can
be missed on routine examination. In some of the patients
tested, a non-organic cause was not part of the differential
diagnosis, as an organic cause for a visual defect was clearly
established. However, a mfVEP obtained to confirm the ex-
tent of the defect indicated that the HVF results exaggera-
ted the extent and/or depth of the defect (18).

Diagnosing and Following Optic
Neuritis/Multiple Sclerosis

When it comes to the diagnosis and treatment of optic
neuritis (ON), the mfVEP has clear advantages over tradi-
tional visual fields and the conventional VEP. It is well
known that patients who have recovered from an attack of
ON can have reasonably normal visual fields. In some
cases, the patients complain of “hazy” or “fuzzy” vision in
parts of the visual field, although the HVF can appear nor-
mal in these regions. Patient 2, a 39-year-old man, had an
acute attack of ON in October of 1999. The diagnosis of MS
was confirmed with neurologic, spinal fluid, and MRI ex-
aminations. The HVF and mfVEP performed 7 days later
confirmed a moderate to marked inferonasal defect OD
(14). Within 4 weeks, his vision improved and his HVF ap-
proached normal. The patient, however, still had some com-
plaints and we have been following him with the mfVEP.
Both mfVEPs and HVFs (Fig. 4A) were obtained 10
months after the onset of ON. His HVF was normal (Fig.
4A, left panel). However, the mfVEP OD was markedly
delayed in some regions. Examples are shown by the inset
in Figure 4A, right panel. The responses (blue) from the OD
are clearly slower than the responses (red) from the OS.
Notice that the interocular mfVEP plot (Fig. 4A, right
panel) is showing abnormalities while the monocular HVF
is essentially normal (Fig. 4A, left panel). [The monocular

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A given patient can show a range of normal and abnormal mfVEP responses within the recovered HVF field. It is not uncommon to see regions with normal amplitude and timing, regions with normal amplitude but abnormal timing and regions with depressed amplitude and abnormal timing in the same patient (14,27). These findings suggest that the mfVEP is detecting local demyelination, as the regions with delays can be adjacent to regions with responses with normal amplitude and latency. These findings also explain the range of results reported in the conventional VEP literature. For patients who have recovered from ON, the conventional VEP is often abnormal, but it can appear normal in cases where MS has been documented on MRI and/or neurologic examinations (1,2,28,29). Because the conventional VEP is the unequal sum of the responses from different parts of the field, the result will depend on how the normal and abnormal field regions are weighted.

Clearly, the mfVEP has the advantage over the conventional VEP and the HVF in following patients with ON. The mfVEP should prove useful in assessing the efficacy of drugs designed to impede the course of MS.

The mfVEP also can help in the diagnosis of ON/MS. Although the diagnosis of ON can usually be made based upon the patient’s history and HVF, a small percentage of patients with ON can present with swollen discs but without pain. In these cases, it is important to distinguish between ON, ischemic optic neuropathy (ION), and a compressive lesion. Patient 3 is a 44-year-old woman who noticed blurred vision in the OS 6 days prior to her first test. The HVF showed a central scotoma breaking out above fixation.
Two weeks later, both HVFs and mfVEPs were obtained. The HVF showed a paracentral defect OS (Fig. 4B, left panel). There is a much larger region of abnormal responses on the interocular mfVEP plot (Fig. 4B, right panel). In addition, the clear delays in the mfVEP confirm that the problem is ON/MS. Her mfVEPs are shown in Figure 2C, as well as in the inset in Figure 4B. Note that some regions show severely diminished amplitudes (solid dot), some show somewhat diminished amplitudes with large delays (asterisks), and other regions have normal responses (plus symbols).

This case can be contrasted with Patient 4, a 52-year-old man who noted a sudden onset, painless loss of vision in the OD. His HVF revealed an inferior altitudinal defect and he was found to have disc swelling OD and a small cup OS. Visual acuity and color vision were preserved in the affected eye. Both his HVF (Fig. 4C, left panel) and the interocular mfVEP (Fig. 4C, right panel) probability plots show an extensive defect in the inferior field. His mfVEPs are shown in Figure 2D, as well as in the inset in Figure 4C. Unlike the patients with ON, the mfVEPs from patients with ION, when present, are not delayed. As an example, examine the responses marked with asterisks in Figure 4C (right panel). Eight months later, his acuity and visual fields remained stable. Although disc swelling had resolved, he developed segmental optic atrophy. His clinical course and mfVEP are consistent with ION.

**Confirming Unreliable or Questionable Fields**

Some patients who have difficulty with the HVF are easy to spot as the reliability indices (percent of fixation losses, false positives, and false negatives) are abnormal. Although occasionally poor visual field takers are also poor mfVEP subjects (18), the mfVEP provides a viable alternative for most of these patients. Patient 1, discussed above (Fig. 3), provides an example. He had 87% (OS) and 50% (OD) fixation losses, far exceeding the criterion for an unreliable field taker.

The neuro-ophthalmologist is often faced with an apparent defect on the HVF, but with insufficient evidence to feel comfortable making a diagnosis. In such cases, the mfVEP provides another topographical map that can be used to confirm or refute the defect detected on the HVF. In our experience, this is one of the most important uses of the mfVEP in neuro-ophthalmology.

Patient 5 is a 70-year-old man who was a glaucoma suspect. His HVF OD appeared normal, but seven HVFs OS obtained over a 19-month period occasionally showed abnormalities. The HVF obtained in October 2001 (Fig. 4D, left panel) showed defects that were more subtle than those seen on some of the earlier tests. The field obtained a few months later (Fig. 4E, left panel) suggested a defect in the lower field (green ellipse). The mfVEPs (right panels of Fig. 4D and E) were obtained on the same days on which the fields were obtained. Notice that defects are seen on the mfVEP plots in both the upper and lower fields on both test days. Some of the responses from these regions (green ellipses) are shown in the insets of Figure 4D and E along with responses from regions with normal mfVEPs (purple ellipses). The mfVEP confirms glaucomatous damage.

Patient 6 is a 52-year-old man with peculiar bitemporal scotomas and with a strong family history of glaucoma. Since March of 2001 he was aware of a problem just off fixation, and just below the midline, in the left visual field of his OS and the right visual field of his OD. He first noticed that he was unable to see the “O” in a vertical HOTEL sign in contralateral and corresponding locations of both eyes. His 24-2 HVFs (Fig. 5A) show a small defect OD and the 10-2 HVFs (Fig. 5B) show small defects OU. Whereas glaucomatous damage was suspected, a chiasmal lesion or demyelinating event could not be ruled out. Bilateral defects appear on the mfVEP (Fig. 5C), closely matching the topography of the defects on the HVF. The responses show no sign of delays as might be expected with MS.

**Following Disease Progression**

As mentioned above, the mfVEP shows good repeat reliability (18,20,22,30). The records in Figure 4D and E provide an illustration. These mfVEP responses were obtained 3 months apart. This reliability allows the mfVEP to be used as a means to follow disease course, a particularly important resource when the HVFs cannot be trusted.

**Combining mfVEP with mfERG**

Multifocal VEP may be combined with multifocal electroretinography (mfERG) in diagnosis (31). In the work-up of obscure visual loss, patients will have a mfVEP first and then be dilated to have a mfERG on the same visit. If the mfVEP and the HVF are both abnormal, a mfERG is used to exclude outer retinal damage. This combination of tests has frequently been helpful in distinguishing between branch arterial occlusions and ION, both of which can cause altitudinal visual field defects. In effect, the mfERG establishes the organic origin of the HVF defect, confirms the extent of the field loss, and may suggest its cause (with delayed responses in the case of ON), while the mfERG rules out damage to the outer retina.

**SOME LIMITATIONS**

Like the HVF, the mfVEP is not without its limitations. Some are similar to those of the HVF. For example, as in the case of the HVF, lids can occlude the field of view, care needs to be taken to correct for refractive error, and eye movements should be monitored. Three problems with the mfVEP are of special concern.
Spatial Resolution

As the case in Figure 5 illustrates, the spatial resolution of the mfVEP can rival the 10-2 HVF. In the periphery, however, the spatial resolution can be relatively poor. The sectors in the peripheral ring are over 7° in width. Considering the fact that one would like to see at least two, if not three, contiguous abnormal points to confirm a defect (16, 18, 19), it is possible to overlook reasonably large, focal defects if they are restricted to the outer ring (beyond about 15°). For example, it is difficult to detect the blind spot in most recordings (18).

Poor mfVEP Subjects

Just as there are patients who are unreliable HVF takers, there are patients who can not be tested with the mfVEP. Patients who refuse to cooperate or who go to sleep may be difficult to test on either the HVF or the mfVEP. In our experience, however, most patients who are poor HVF takers are able to perform the mfVEP test (18). On the other hand, there are some good HVF takers who do not produce usable mfVEP recordings. Relatively few patients have mfVEPs too poor to be of clinical use. In these cases, the responses are difficult to discern because of a high noise level secondary to a large alpha contribution or muscle tension.

Eccentric Fixation

As with HVF testing, it is important to monitor the patient's eye position. An eye camera or direct visualization of the eye should be used to assure that fixation is steady. Unsteady fixation can cause diminished responses in the center of the field (18, 32, 33). Monitoring the eye, however, will not assure that the fixation is accurate. Some patients with central visual problems can have eccentric fixation. Figure 6 shows the effects of a 3° fixation error. A control subject was instructed to maintain steady fixation down and to the left by 3° for the OD while the OS was tested with central fixation. Compared with the control condition (Fig. 6A, B), the eccentric fixation condition (Fig. 6C, D) showed apparent defects in both eyes on the interocular probability plot. It is relatively easy to attribute these “defects” to eccentric fixation. The probability plot shows smaller responses in diagonally opposite parts of the field. That these symmetrical defects are due to eccentric fixation is confirmed by examining the responses from near the midline. Some of these responses (see inset in Fig. 6D) show a polarity reversal between the two eyes. In sum, it is important to monitor eye position to avoid false positives due to unsteady fixation and to scrutinize the mfVEP plot and responses to avoid false positives due to eccentric fixation.

SUMMARY

The clinical value of the mfVEP lies in its ability to detect small abnormalities in visual signal transmission from centric and eccentric field and to provide a topographical display of these deficits. Together with the mfERG, it can provide objective evidence of visual pathway pathology. As with the mfERG, the value of
FIGURE 6. The problem of eccentric fixation. A. The interocular mfVEP probability plot for a control subject fixating at the center of the stimulus when testing OU. B. The 60 mfVEP responses corresponding to the probability plot in A. Responses in the inset are of the same polarity and appear normal. C. The interocular mfVEP probability plot for the same subject instructed to fixate down and to the left by 3° when testing OD and fixating in the center when testing OS. D. The 60 mfVEP responses corresponding to the probability plot in C. Responses in the inset show clear polarity reversals and amplitude differences between the two eyes. Eccentric fixation can give the appearance of an abnormality in an otherwise normal eye.

The multifocal technology is still in its infancy. Better methods of signal analysis, more effective stimuli, and improved recording conditions will soon be developed (18). It is not yet a widely accessible device. Although recording high quality mfVEPs is not difficult, it s requires a technician trained in electrophysiological recordings. Commercial software for adequately analyzing the mfVEP is not yet available in most countries, including the United States. Until the analysis is standardized, the interpretation of the mfVEP requires experience and is best performed by an experienced electrophysiologist familiar with the mfVEP test in concert with a neuro-ophthalmologist.

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Adelbert Ames and the Dartmouth Eye Institute

Susan M. Pepin, MD

The striking of friendships and the meetings of minds have yielded advances in many fields. For example, there is the meeting of Frans Cornelius Donders and Albrecht von Graefe in London in 1851, which joined knowledge of physics and optics to clinical ophthalmology. Another gathering occurred in Hanover, New Hampshire, early in the twentieth century. The founder of the Dartmouth Eye Institute (DEI), Adelbert Ames II (Figs. 1–3), drew leaders in ophthalmology to this rural hamlet and sparked excitement in vision research.

The story of the DEI stands as an example of collaboration among investigators from multiple fields that began as one individual’s quest to understand what influences how we see. From 1921 to 1947, Ames brought together, among others, Walter Lancaster, Kenneth Ogle, Arthur Linksz, Paul Boeder, Hermann Burian, and Alfred Bielschowsky. Little evidence marks its erstwhile prominence, but the DEI used a collection of diversely trained researchers committed to furthering the understanding of vision and perception. Many of the topics explored by this fortuitous assemblage of people flourish in modern vision research.

Ames came from a distinguished family. His maternal grandfather, Benjamin Butler, was a general and governor of Massachusetts. General Butler ran unsuccessfully for President in 1884. His father, Adelbert Ames I, had been a general in the Civil War and later a Mississippi governor and United States senator.

As a Harvard undergraduate, Ames took courses from William James and George Santayana. After completing Harvard Law School, he became disillusioned with legal practice and became an artist. Inspired by his sisters, who were painters, he tried “to make exact color reproductions of scenes” (1). With his sister Blanche Ames, he devised a color notation system consisting of more than 3,300 different color variations (1). (By comparison, the influential system created by the artist Albert Henry Munsell, and still used by clinicians and artists, contains only 1200 color variations [2].) While traveling around New England painting landscapes and sculpting, Ames’ analytical mind contemplated the relationship between what one sees and what can be represented in art. How, he wondered, does the visual system reproduce the reality of the environment?

To approach the problem, he sought to understand the basics of image formation in the eye by studying its optical

FIGURE 1. Adelbert Ames II, founder of the Dartmouth Eye Institute (circa 1940). (Courtesy of Dartmouth College Library)
characteristics. In 1914, he accepted a research fellowship with John Wallace Baird, a psychologist at Clark University, and began more formal work in visual perception. In 1919, after a stint in the United States Army, where he gained experience designing instruments, Ames came to Hanover, New Hampshire, to consult with physics professor Charles A. Proctor. Ames, his sister Blanche, and Proctor worked on a "binocular camera" which would simulate the superimposition in the brain of the retinal images seen by each eye.

In 1921, Ames and Proctor published their first paper, "Dioptics of the Eye," in the *Journal of the Optical Society of America* (3). The article attracted so much attention that Ernest Hopkins, the president of Dartmouth College, created the Department of Research in Physiologic Optics. Ames was elected Professor of Research in Physiologic Optics and given a Master of Art Degree by Dartmouth College later that year.

When Ames and Proctor began their collaboration, the geometry of binocular vision was an area of active interest. It was during this time that Gordon H. Gliddon, a lens designer for Eastman Kodak Company, arrived in Hanover to enroll as Ames’ graduate student. With Gliddon’s help and expertise in lenses, Ames built a camera whose lens could simulate various optical aberrations of the eye. The goal was to produce photographs that could guide artists in portraying a scene as the human visual system allows it to be perceived.

Ames’ personal excitement about vision research was drawing other colleagues and graduate students to Dartmouth. In 1930, Kenneth N. Ogle submitted his Ph.D. thesis under Ames with the title “The Resolving Power of the Human Eye.” The combined results of these researchers led to the establishment of the Dartmouth Eye Institute (DEI) as separate from the Department of Physics (Fig. 4). A growing team of investigators shifted from exploring the optical properties of a single eye to the problem of binocular vision and space perception.

The influence of retinal disparity on binocular depth perception had been studied by Panum and others in the early and mid-nineteenth century. In 1858, Panum had described the range of fixation with minimal retinal disparity over which fusion of two images can occur. By 1928, Ames and his colleagues had pursued an understanding of the influence of binocular vision on perception. In particular, Ames recognized that depth perception was not the simple fusion of two images focused on each retina, and that when
the two retinal images do not match, distortions of space can result. He believed that prisms could correct horizontal and vertical misalignments of the two eyes, but wanted to better correct what he called “a turning movement of the eye about the visual axis itself” (4). He gained a patent for an instrument he called the Lyman Dingbat, a device mounted on spectacles and designed to correct rotational mismatches between two eyes (Fig. 5).

The DEI’s early fame came from the development of instrumentation and techniques for the measurement and correction of anomalies in the size and shape of ocular images. Theorists such as Donders (1864) had appreciated that large differences in image size from anisometropia make binocular vision difficult or impossible. The DEI group fastened on this problem and used mathematical models to determine some of its causes, including unequal optics between the two eyes. Meticulous clinical experiments were performed to verify the anomalies. The technology developed was used to evaluate patients and correct the phenomena. The term “aniseikonia,” combining the three Greek words meaning “not equal image,” was coined in 1932, based on input from Harvard professors Charles Gulick, professor of classics, and Walter Lancaster, MD, a leading ophthalmologist who would later join the Dartmouth group.

DEI researchers reported evidence that image size differences as small as 0.5% to 2% might cause problems with fusion and that patients perceiving this image size difference might experience distortions of space and depth (5). Ames, Ogle and Gliddon believed that people with aniseikonia might not recognize the distortions but would have “asthenopic symptoms.”

In 1932, Ames, Gliddon, and Ogle published “Size and Shape of Ocular Images, Part I” in the Archives of Ophthalmology (6), describing the theory and methods used in their new ocular measuring instrument, the eikonometer, to determine differences in the size and shape of images perceived by the two eyes (Fig. 6). The instrument design grew out of the theory of Hering’s longitudinal horopter apparatus and Tschernak’s binocular devise developed in 1930. The authors made an argument for the impact of this size and shape difference on binocular depth perception and the impact of a disturbance in binocularity on “mental causes of discomfort” (6). The second part of this article, published a month later by DEI researchers Elmer H. Carlton, MD and Leo F. Madigan, OD, reported case studies proving that innumerable symptoms could be relieved by correcting refractive errors and interocular image size differences (7).

Carlton, who had graduated from Dartmouth Medical School in 1897, served as a clinical instructor in otolaryngology and ophthalmology until he lost his right arm to an infection developed while he was operating. With his left arm, he became an expert refractionist and remained at the DEI from 1928 until it closed. Madigan had been a former student under Gliddon at the Rochester School of Optometry. These collaborators alleged that aniseikonia causes
FIGURE 6. Leo Madigan OD experimenting at the DEI with an early model of an eikonometer (circa 1934). (Courtesy of Dartmouth College Library)

mysterious and incurable headaches, nervousness, bodily fatigue, stomach disorders, dizzy spells, carsickness, and unaccountable drowsiness. They reported that correction of image size differences brought complete relief of symptoms to 20% of patients, partial relief to 60%, and no relief to 20% (7).

According to Ames and his colleagues, retinal image asymmetry could be produced by retinal anatomic differences or by the lens system of the two eyes. The accommodation of one eye might differ from that of the other eye, or one eye alone may have astigmatism. When correction of the differences required lenses with powers greater than 0.50 diopter, there was a difference in the exterior focal distance that would blur one image. Ames and Gliddon developed aniseikonic lenses, submitting in 1929 a patent based on a telescopic combination of plates to allow the enlargement of an image on the retina along one axis to equalize dimensions without alteration in the vergence of light. Spectacles could be individualized for each patient based on measurements that would equalize the nodal points in the two eyes. Eyeglasses were made with multiple and superimposed lens elements to correct changes in vergence and retinal dimensional inequality (Fig. 7).

Laid out in more than a hundred subsequent publications in such journals as the American Journal of Ophthalmology and the American Journal of Optometry, the DEI's work became the premise for the instruction in aniseikonia in optometry and ophthalmology clinics and academic departments across the United States. In 1933, Ames and Gliddon were awarded a bronze medal by the American Medical Association for their work on aniseikonia (Fig. 8).

FIGURE 7. Iseikonic lenses produced in 1987. The patient had 2.50 diopters of astigmatism OS. Multiple plus or minus lenses were cemented together on the edges in iseikonic lenses to allow not merely focusing of light rays but equalization of image size on the retina of the two eyes.

did not uncover all the abnormal physiology that might cause symptoms. Thousands of patients from all over the world were drawn to little Hanover, New Hampshire in the hope that detection and correction of aniseikonia would obliterate their symptoms. DEI exponents practiced in Boston, New York, Baltimore, Washington DC, Atlanta, and San Francisco (8).

Perhaps the most famous ophthalmologist to work at the DEI was Dr. Alfred Bielschowsky (Figures 9–11). A well-known European ophthalmologist, Bielschowsky had studied under Drs. Ewald Hering and Carl Sattler in Leipzig, Germany. Early in his career, he became the director of the Eye Clinic at the University of Breslau and published the first sensory description of monocular diplopia and later many articles on ocular motility disorders. In 1934, the "pope of strabismus" accepted an invitation to visit the United States from Arnold Knapp MD, an ophthalmologist and the editor of the Archives of Ophthalmology.

On his tour of the United States, Bielschowsky met Ames, who invited him to visit Hanover and the DEI. Bielschowsky was offered the position of clinical director of the DEI. At first he decided to return to Breslau, but as a Jew, he became a target of anti-Semitic demonstrations outside his office and in his lectures. He later accepted the DEI offer and returned to Hanover.

The presence of Bielschowsky augmented the scientific reputation of the DEI. "Herr Doktor" spent a productive 5 years examining patients, performing surgery, and publishing his comprehensive "Lectures on Motor Anomalies," including "The Etiology of Squint" and "Functional Disturbances of the Eyes" (9,10). Although he enthusiastically supported the development of "evidence of a causal connection between aniseikonia and the deficiency of fusion" as a cause of strabismus, Bielschowsky's own involvement in aniseikonia was limited (11). Early in his time at the DEI, he brought his former student Dr. Werner...
Herzau to Hanover. Herzau had trained in Prague and later worked under Bielschowsky in Breslau. When Herzau decided to return to Germany in 1935, Bielschowsky invited another European-trained ophthalmologist, Dr. Hermann Burian from Prague, to join the group (Fig. 12). Burian stayed at the DEI for 10 years before leaving for a private practice in Boston, and, in 1951, for the University of Iowa, where he continued to contribute greatly to the field of ophthalmology. Bielschowsky died suddenly after attempted pneumoencephalography in New York as part of the diagnostic investigation of a brain tumor. His grave lies in the cemetery in the center of the Dartmouth College campus.

In the autumn of 1940, Lancaster (Fig. 13) agreed to replace Bielschowsky as the clinical director of the DEI. While many others had been skeptical of the work at the DEI, Lancaster had been involved with the group for many years while in practice in Boston. His wife Emma Winter was a descendant of Eleazer Wheelock, the founder of Dartmouth College. Lancaster found that he had little influence on the direction of DEI research or policy and resigned after just 2 years to return to his practice in Boston.

Over the course of almost 20 years, members of the DEI (Fig. 14) collaborated under Ames’ direction to overcome technical and theoretical challenges involved in understanding the physics, physiology, and psychology of vision. In their research synopsis for the staff bulletin in 1941, they wrote collectively:

“As civilization advances, life increasingly depends on the efficiency of our space-perception capacity. Piloting airplanes and driving motor cars are examples...”
of modern activity placing increasing dependence upon this function of vision. The most important contribution made by the Dartmouth Eye Institute has been its advance in the basic knowledge of space perception. Dartmouth’s discoveries of such basic scientific laws and its application of these laws to the relief of human suffering and in the individual’s occupational capacity, have in turn led to the Institute’s collaboration with instrument and lens makers to make this new knowledge widely available.” (8)

Despite the enthusiasm and efforts of the researchers, financial support for the DEI was always a problem. The Rockefeller Foundation contributed funding in the early years. But the combination of Ames’ shift in interest away from the clinical work of the DEI, postwar changes, and hierarchical interplay between Dartmouth College, the Medical School, and the Hitchcock Clinic made for an uncertain fiscal environment. Lack of independent support and politics within the university eventually led to the DEI’s closure in 1947. David C. Bisno, MD has written an extensive description of the DEI, attributing its closure to Dartmouth College president Hopkin’s greater loyalty to the undergraduate college than to the graduate schools (12).

In the DEI’s final years, Ames and some of his colleagues shifted their interests toward psychology. While this shift reflects Ames’ broad interest in perception, it may also be the result of the inability of his optical systems and isokonic lenses to correct or explain visual experience. Ames’ later writings discuss an “assumptive world” based on an internalized perceptual system, a reminder of his original quest to understand the interplay between perception of reality and art. From the middle of the 1930s until his death, he studied visual illusions, collectively published under the title “Ames’ Demonstrations in Perception” (13).
moved freely between historically unrelated fields, a skill that might have served him well today with the current emphasis on multidisciplinary scholarship. In an example of his interest in the philosophical and social implications of vision, he wrote that "the insights gained in the study of visual sensation can serve as indispensable leads to better understanding and more effective handling of the complexities of social relationships" (14). In his later years, Ames was trying to elucidate the interdependencies between perception, action, and purpose. For example, he developed "demonstrations" of trompe l’oeil for the psychology laboratory that challenged perceptual interpretation by creating illusions. With the creation of the "leaf room," he hoped to achieve an environment with a minimum of monocular depth cues. In a cube of wire mesh mounted on a wire frame, oak leaves were used to cover all but one open side (Fig. 15). Ames then used eikonic lenses to enlarge the image on the retina along one axis without altering the optical properties of the two retinal images. With this protocol, he studied binocular space perception with altered binocular disparities without affecting other distance clues (13). His work had a strong influence on the evolution of psychology, particularly through his relationship with Hadley Cantril, PhD, professor of psychology at Princeton University.

Ames died in Hanover in 1955, after receiving a Doctor of Laws degree from Dartmouth College in 1954 for his significant influence as a "lifelong student of human perception."

Reminders of Ames and the DEI linger in Hanover. There is the patient who brings an odd set of spectacles to the clinic. A past employee of the DEI fondly recalls the enjoyment several researchers would get from sending a newly hired nurse on an urgent errand to the hospital storage rooms in search of one hundred feet of Fallopian tube. But the DEI’s work on aniseikonia has not endured within

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**FIGURE 15.** The Leaf Room (circa 1939). Ames developed the Leaf Room, lined with leaves, to eliminate the cues for perspective interpretation so that the observer in front of the room would have to depend primarily on binocular vision or stereopsis for three-dimensional perception. When eikonic lenses were introduced to alter the two retinal images, the observer would see the room as tipped, with the floor and ceiling raised or lowered. The room can still be found in the basement of the Hopkins Center at Dartmouth College. (Courtesy of Dartmouth College Library)
the scientific or clinical arenas of ophthalmology. Claims of curing so many nonspecific symptoms with eikonic lenses seem over zealous today. A small amount of aniseikonia is now considered common and of no clinical consequence. The mathematics involved in understanding or correcting large differences in the size of optical images of the two eyes has disappeared from ophthalmology training, perhaps because advances in contact lenses and refractive surgery have eliminated large interocular image size disparities.

The legacy of the DEI lies rather in the productive effort of a cohort of researchers devoted to understanding vision. Ames propelled the careers and research efforts of many others who spread out from Hanover to make substantial contributions in the fields of optics, visual perception, and psychology.

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Approximately 5250 abstracts were presented at the Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO), Fort Lauderdale, FL, May 4–9, 2003. The abstracts, available on www.arvo.org, are referenced by program number (\#).

NEURO-PROTECTION

New approaches to neuro-protection targeted the optic nerve or the retinal ganglion cells (RGCs) in animal models of optic nerve damage and in patients. Lomerizine, a diphenylmethylpiperazine calcium antagonist, was shown to enhance retinal ganglion cell survival induced by optic nerve damage (\#108). In another study, trans-corneal electrical stimulation was shown to enhance the survival of axotomized retinal ganglion cells in adult rats (\#109). In another study from Germany, the authors concluded that there was inhibition of calcium-activated neutral cysteine proteases by calpain inhibitor MDL-28170, which may offer neuroprotective effects after an excitotoxic lesion (\#110). Copolymer 1 (Copaxone), an FDA-approved drug for multiple sclerosis (MS), was shown to rescue at least 50% of the potentially doomed retinal ganglion cells following intraocular pressure-induced death. This drug has the potential for use as a therapeutic vaccination in cases of acute optic nerve damage following high intraocular pressure (\#112). Theanine, topical brimonidine purite (Alphagan-P), and minocycline were found to protect retinal ganglion cell damage in rats (\#119, \#120, \#124). Neuroprotective effects of the potent anti-inflammatory cytokine interleukin-10 (IL-10) were shown to inhibit apoptosis of retinal ganglion cells. It was postulated that IL-10 may exert its effect by modulating nuclear factor kappa-B activity or by inhibiting the synthesis of proinflammatory cytokines such as TNF-alpha, both of which play an important role in cell survival (\#125).

OPTIC NEUROPATHY

Sleep apnea was suggested as one of the risk factors in patients with ischemic optic neuropathy (\#625). A rat model of photoembolically-induced non-arteritic ischemic optic neuropathy (NAION) appeared to spare the retinal vasculature, as evidenced by normal electroretinogram (ERG) recordings (\#622). Gene expression studies in a similar rat model were shown to correlate with retinal ganglion cell loss (\#624). Serum uric acid, a natural antioxidant, was found to be lower in patients with acute optic neuritis and MS than in controls; it may be a marker to distinguish optic neuritis from other optic neuropathies (\#630). Among patients with sarcoid optic neuropathy, early withdrawal of corticosteroid treatment was associated with relapse and the need for additional immunosuppressive therapy to maintain vision (\#637).
IMAGING

There were several papers that discussed the reproducibility of optic nerve head parameters and retinal nerve fiber layer thickness (RNFL) measurements using the new optical coherence tomography 3 device (OCT 3) (#3384, #3394, #3396, #3639). The OCT 3 has the potential of detecting changes prior to their detection with achromatic automated perimetry (#3392). Retinal thickness was found to be 10% greater when measured histologically in rabbits as compared with OCT measurements and this variation resulted from the fact that the OCT measures the optical properties of the retina rather than the actual thickness of the RNFL (#3639). Mean muscle index of all six extraocular muscles using A and B scan USG and the BVI Quantel Cinescan S program aids in the differential diagnosis of patients with thyroid eye disease; the authors found a high incidence of involvement of the superior rectus muscle (#3657).

PSEUDOTUMOR CEREBRI

In a retrospective study of 72 eyes with pseudotumor cerebri (PTC), the authors found sequential disc photographs to be a sensitive method in monitoring disease progression (#610). Measurements of optic nerve sheath diameter using B-scan USG seemed to be a good non-invasive and indirect measure of raised intracranial pressure in patients with PTC (#611). Analysis of perfusion-weighted MRI and MRA in patients with PTC revealed marked hypoperfusion of subcortical white matter (#612). Positron emission tomography (PET) can provide functional information not attainable with MRI or MRA. PET imaging in a patient with PTC and vision loss (with normal brain MRI) revealed a bilateral decrease in the glucose uptake in the visual association areas (Broca's area 19, dorsal visual stream). Postoperative PET scans following optic nerve sheath fenestration surgery demonstrated a bilateral increase in uptake along the occipital, temporal, and parietal visual association areas that correlated with significant visual improvement (#2725).

OPTIC NERVE

Quantitative analysis of optic disc parameters using Heidelberg retinal tomography in patients with optic nerve head drusen with and without visual field loss demonstrated that the disc and rim areas were significantly larger in patients with visual field loss than in those without visual field loss. It was hypothesized that the drusen reach a critical size at which compression damage of axons and corresponding field defects finally occur (#615). Analysis of visual field defects in patients with congenital optic nerve tilting or enlarged optic nerve cups disclosed features typically seen in patients with optic nerve hypoplasia(#617). Optic nerve hypoplasia was found in about 10% of patients with anhidrosis with or without foveal hypoplasia (#620). Strabismus and anisometropia were the most common clinical signs in 20 patients with Morning Glory syndrome, and B-scan USG demonstrated a new finding called the “overhanging glial tissue sign” (#621). Chronic ischemia in the monkey optic nerve induced by infusion of endothelin-1 to the nasal superior optic nerve resulted in a preferential damage to the temporal superior region of the optic nerve (#3325). Immunohistochemical studies of cadaver optic nerves in the region of the lamina cribrosa demonstrated increased mitochondrial density; the authors suggested that this finding indicates increased energy requirements in this region. It may also why optic neuropathy occurs in mitochondrially-inherited diseases (#626). In an experimental study in pigs, intravenous acetazolamide, in addition to carbogen breathing (95%O2+5%CO2), significantly increased oxygenation of the optic disc, probably due to the vasodilatory effect of elevated systemic PaCO2 (#1298).

LEBER HEREDITARY OPTIC NEUROPATHY

A separate session dedicated to Leber's Hereditary Optic Neuropathy (LHON) detailed the results of a comprehensive one-year follow-up examination of the 300-member homoplasmic 11778 LHON pedigrees of seven generations described in rural Brazil. The authors found that carriers of LHON had subtle findings including disc edema, blood vessel telangiectasias, nerve fiber layer edema, reduced nerve fiber layer measurements (#939), mild visual field defects (# 935), tritan or deutan color vision defects (#940), and prolonged latencies in the pattern-reversal visual evoked potentials (#936). Patients with severe visual loss continued to demonstrate low grade deterioration over time.

Administration of complex II substrates or the human gene for mitochondrial superoxide dismutase (SOD2) did not significantly improve LHON cybrid cell survival and suggested that other reactive oxygen species or reduced ATP synthesis may play a role in cellular injury and optic neuropathy in LHON (#941). In another paper, the authors showed that the oxidative injury induced by Complex I deficiency is protected with adeno associated virus-mediated gene transfer of human SOD2 and concluded that that this approach may be used in the future to treat patients with diseases like LHON or MS (#627, #628). Segregation analysis of 128 maternally-related individuals with LHON indicated the existence of a nuclear modifier gene that could explain variable penetrance within the same family (#937).

There were no significant differences in the circulating levels of total antioxidants, lipids peroxidation products, IL-3 and TNF-alpha in male and female LHON patients and non-affected carriers. However, there was a significant elevation of circulating and neuron-specific enolase levels in male carriers when compared with normal
male controls. Neuron-specific enolase levels may be a good indicator of retinal ganglion cell and optic nerve stress degeneration (#938).

EYE MOVEMENTS
In an attempt to find a reproducible and standard measure of ocular motor ductions in clinical trials, the Kestenbaum test (using a ruler to measure the ductions) was found to be less variable than a cervical range of motion device (CROM) (#1931). Deep brain stimulation of the thalamus in patients with Parkinson’s disease minimized the tremor and improved fixation stability and eye-head coordination movements (#1935). In a prospective study, all 25 CPEO patients with cytochrome c oxidase (COX)-deficient fibers presented with exotropia, relative sparing of downgaze, and the degree of diplopia was proportional to the proportion of COX-deficient fibers in the muscle biopsy (#1947).

ELECTRORETINOGRAPHY
Multifocal electroretinography (mfERG) may emerge as the best method to detect early retinal toxicity in clinically symptomatic and asymptomatic patients on long-term chloroquine/hydroxychloroquine retinopathy. MfERG showed a significant decrease in the PI amplitude in the foveal and paracentral rings (#2701). The ERG photostress test, using focal 41 Hz ERG, was found to be effective for early detection of macular disease and was unaffected by media changes (#1899).

PUPIL
Alterations in the pupil size were shown to alter the temporal modulation sensitivity (TMS) and absolute light sensitivity (ALS) across the central visual field. Dilated pupils (6mm) resulted in higher sensitivities than did smaller pupils (3, 4.3mm) for both of these visual assessment parameters (#4095). The relationship between parameters of the pupillary light reflex and the corneal illuminance after 20 minutes of adaptation for each illuminance level was investigated in 23 normal subjects. The authors found that the amplitude of pupillary constriction changed with the adaptation illuminance level significantly in the adaptation light range from 60–400 ft-cd. It was concluded that the adaptation illuminance (in ft-cd) must be considered when quantitatively measuring the parameters of the pupillary light reflex (#4077). Alterations of the pupil diameter (using mydriatics and miotics in normal subjects) influenced the latency but not the amplitude of multifocal visual evoked potentials (mfVEP). The results suggest that even with pharmacologically altered pupil size, the mfVEP can be used to assess diseases that affect signal amplitude, but the interpretation of latency must be used with caution as a borderline conduction defect with a dilated pupil may appear normal (#4118).

PERIMETRY
The new frequency doubling perimetry (FDT2) 24-2 testing strategy provides a screening and quantitative visual field parameter for optic nerve, chiasmal, and post chiasmal disorders, and was found to correlate well with HVF II SITA Standard 24-2 program (#1951, 1956). Patients with recovered optic neuritis showed better visual fields than predicted by nerve fiber layer thickness, perhaps as a result of a compensatory mechanism not present in other optic neuropathies like glaucoma, AION, and compression (#1959).

SCANNING LASER OPHTHALMOSCOPY
The scanning laser ophthalmoscope was found to be a useful tool in the evaluation of suspected psychogenic visual loss as it could document patient fixation and test visual acuity under direct visualization (#1963).

ORBIT
The integrated hydroxyapatite implant reduced implant migration but increased the rate of conjunctival dehiscence when compared with the non-integrated implants (#2216). In another study, extrusion of the implant was only seen with the glass sphere implants when compared with porous polyethylene and hydroxyapatite implants (#2219). In an experimental study using pediatric porcine anophthalmic sockets, the hydrogel autoexpandable orbital implants provided safer and more reliable stimulation of bony orbital development than did dermis fat grafting (#2226). A graded approach to orbital decompression for dysthyroid orbitopathy resulted in a fairly predictable proptosis reduction; the greatest reduction was seen with a three-wall decompression through a lateral and transcaruncular approach (#2223). Orbital endoscopy using free electron laser allowed better visualization of media using carbon dioxide and it was possible to perform optic nerve sheath fenestration in cadaver eyes using this technique (#613, 614).

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The 6th European Neuro-Ophthalmological Society (EUNOS) meeting was held from June 15 through June 18 in Göteborg, Sweden. The meeting drew 195 attendees from 27 countries. Its organizer, Bertil Lindblom, put together an eclectic program comprised of 51 papers, 37 posters, and 12 invited lectures. The entire set of abstracts for the meeting is published in Neuro-ophthalmology 2003; 27:193–262.

A preliminary half-day session on the first morning was devoted to courses on ocular motility, the pupil, pseudotumor cerebri, and optic neuropathies. The afternoon session consisted of the Ahlberg Lectures, including one on retinal neurobiology given by Berndt Ehinger (Lund, Sweden), one on neuronal generation from stem cells in the adult brain given by Jonas Frisen (Stockholm, Sweden), the son of Lars Frisen (Göteborg, Sweden), and one on the potential use of stem cells for repair in neurodegenerative disease, given by Peter Eriksson (Göteborg, Sweden).

The remaining days consisted of nine sessions commencing with an invited orientational lecture and followed by free papers relating to the topic and a poster session. Here are some of the highlights (Fig. 1).

RETINAL NERVE FIBER LAYER

William F. Hoyt, MD (San Francisco, CA) gave a comprehensive historical review of retinal nerve fiber layer observations in neuro-ophthalmological diagnosis. Many fellows in the audience recognized seminal pictures from their days in training with Dr. Hoyt. Randy Kardon, MD, PhD (Iowa City, IA) discussed the relationship between retinal nerve fiber loss, relative afferent pupillary defect, and visual field loss in optic neuropathies. Eeva Nikoskelainen (Helsinki, Finland) presented studies on OPA1 gene mutations in Finnish families with dominant optic atrophy. This gene on chromosome 3q28 encodes for a GTPase protein related to dynamins. No mutational hot spot has been found and over 60 mutations of this gene have been identified. As such, simple DNA testing can be offered only for families in which the DNA mutation is known. Catherine Vignal-Clermont (Paris, France) discussed different mechanisms of dysthyroid optic neuropathy, including apical compression of the optic nerve by enlarged muscles and orbital fat, optic nerve ischemia, lymphatic and venous stasis, and stretching of the optic nerve. Silvia Muñoz (Barcelona, Spain) presented a patient with radiation optic neuropathy who benefited from hyperbaric oxygen therapy 14 weeks after the onset of visual loss. Robert de Keijzer (Leiden, Belgium) presented four patients who experienced progressive visual impairment after total extirpation of a meningioma in the sphenoid region despite a negative MRI. All four cases experienced visual improvement after surgery disclosed tumor confined to the optic canal. Natalia Serova (Moscow, Russia) examined the natural history of surgical hypophysectomy in 154 patients with pituitary adenoma and found that 81% had visual improvement, 10.8% had no change, and 7.2% had visual loss. Postoperative visual loss was attributed to surgical injury to the visual pathways and their vessels, hematoma, delayed collapse of the tumor capsule, and development of an empty sella.

RETINAL VASCULOPATHIES

In a session dedicated to retinal vascular disorders, Dieter Schmidt (Freiburg, Germany) discussed the pathophysiology of central retinal artery occlusion and the potential role of intra-arterial thrombolysis in the management of this dire condition. He also showed examples of an ultrasonographic halo within the temporal artery in patients with giant cell arteritis. Although he believed that this ultrasonographic finding obviates the need for temporal artery biopsy, some patients can still have disease when the sign is absent. Eberhart Zrenner (Tuebingen, Germany) discussed the molecular mechanism in the complete form of x-linked congenital stationary night blindness, which is caused by mutations in a leucine-rich repeat protein of the NYX protein. S Gedik (Ankara, Turkey) reviewed the use of fluorescein angiography and indocyanine green angiography in showing optic disc hyperfluorescence as the first sign of ocular Behçet's disease. Gordon Plant (London, England) reviewed non-embolic causes of transient monocular blindness, concluding that the general absence of headache and response to nifedipine implicates vasospasm. Klara Landau (Zurich, Switzerland) reported the outcomes following fractionated stereotactic conformal radiotherapy in eight eyes with optic nerve sheath meningioma. Controls consisted of six untreated eyes. Patients and controls had a mean follow-up of 52 months. Visual acuity or visual fields...
FIGURE 1. Some of the notables at the EUNOS meeting 2003. From the left: Lars Frisén (Göteborg, Sweden); Bertil Lindblom, president of the meeting (Göteborg, Sweden); Natalya Serova, organizer of the 2005 EUNOS meeting in Moscow, Russia; Alfred Huber (Zurich, Switzerland), one of the founders of EUNOS; and William F. Hoyt (San Francisco, CA).

improved in six treated eyes; these parameters remained stable in four eyes and worsened in two eyes in the control group, suggesting a short term benefit of treatment. In a study of nutritional optic neuropathy in a United Kingdom cohort, Gordon Plant found that this problem arose in patients of Caribbean descent who followed a vegetarian diet and in Caucasians with alcohol abuse. Kumudini Sharma (Lucknow, India) presented two patients who experienced delayed epistaxis and unilateral visual loss following traffic accidents. The first case developed a central retinal occlusion; the second case lost all vision and developed an afferent pupillary defect with no retinal abnormalities. In both cases, carotid angiography disclosed traumatic pseudoaneurysms of the carotid artery (intracavernous in the first case and projecting into the sphenoid sinus in the second). Dr. Sharma advised that patients with epistaxis and unilateral visual loss should undergo carotid angiography to diagnose carotid pseudoaneurysm, and that the optic neuropathy can result from either compression or ischemia.

OCULAR MOTILITY

Huibert Simonsz (Rotterdam, The Netherlands) presented an historical review of pulley bands dating back to the earliest description by Tenon in 1805. Dr. Simonsz called into question the role of pulley attachments to the orbital wall (which are stiff and inelastic) and suggested that intermuscular membranes and orbital fat may be more important for stabilization of ocular rotations. Nagini Sarvananthan (Leicester, England) presented a prevalence study of nystagmus in Leicestershire estimated to be 0.2 per 1,000. M. Castany (Barcelona, Spain) presented a patient with suprasellar craniopharyngioma treated with yttrium-90 brachytherapy. The patient developed a dorsal midbrain syndrome secondary to yttrium seeding of the fourth ventricle. Tony Pansell (Stockholm, Sweden) presented video-oculography data showing that during prolonged head tilt patients show a gradual drift of the static counter roll toward zero over approximately ten minutes. Frank Proudlock (Leicester, England) combined horizontal eye-head recordings to show that head movement gain during gaze shifts significantly increases with age. Shlomo Dotan (Jerusalem, Israel) described four patients with pseudoglaucomatous cupping secondary to intracranial tumors. Helmut Tegetmeyer (Leipzig, Germany) used video-recordings of eye movements in healthy volunteers to show the strong influence of visual perception on spatial coding of saccadic eye movements and fixation. Caroline Tilikeyte (Lyon, France) found that patients with saccadic lateropulsion systematically directed their saccades toward a common “virtual target.” Saccades were observed to be hypometric relative to this virtual target, suggesting that mislocalization of the target was due to perceptual error in patients with Wallenberg syndrome (Figs. 2,3).

VISUAL FIELDS

Michael Wall, MD (Iowa City, IA) gave an excellent review of currently used perimeters. He examined the relative roles of different perimetric methods for diagnosing and following different diseases, and discussed new strategies to increase sensitivity and reduce variability. Jayne Best (London, England) presented controversial evidence that visual field defects secondary to vigabatrin are idiosyncratic and do not progress despite continuing use of the medication. Because of the short follow-up, however, these findings may simply reflect the relative insensitivity of perimetry to small degrees of progression. Hans Fledelius (Copenhagen, Denmark) showed that patients with chiasmal lesions are often unable to read the visual acuity chart.

FIGURE 2. Jonas Frisén, Karolinska Institute, Stockholm, Sweden (left), who delivered an invited lecture entitled “Generation of Neurons from Stem Cells in the Adult Brain,” with his father Lars Frisén.
monocularly despite little or no perimetric defect, suggesting that chiasmal lesions produce some degree of visual hemineglect. He suggested that neuroimaging be considered in patients who exhibit this monocular letter reading deficit in the temporal visual field. Simon Hickman (London, England) presented two cases with junctional scotomas that showed MRI gadolinium enhancement of the posterior intracranial optic nerve, suggesting that the notion of Wilbrand's knee still has clinical application. Anthony Arnold, MD (Los Angeles, CA) described seven patients who had inferotemporal arcuate field defects associated with focal superior segmental optic hypoplasia. Only one case was associated with maternal diabetes. Ulrich Schiefer (Tuebingen, Germany) analyzed junctional scotomas in patients with chiasmal lesions with respect to their neurodevelopmental underpinnings. Helmut Wilhelm (Tuebingen, Germany) discussed the value of binocular perimetry in distinguishing organic from non organic hemifield defects.

COLOR VISION

Gordon Plant reviewed historical aspects of color vision as applied to current neuro-ophthalmologic diagnosis. Pinar Aydin (Ankara, Turkey) found that during occlusion treatment of amblyopia, visual acuity shows a faster improvement than color rivalry suppression, and concluded that color rivalry suppression should be used in deciding when to stop occlusion treatment. John Barbur (London, England) found that a new motion-based color vision test detects abnormalities in those who show no deficit on other color vision tests and have only minimal deficiency on the Nagel anomaloscope.

PUPILS

Fion Bremner (London, England) found that patients with generalized autonomic neuropathy have a pupillotonia that is symmetrical, with relatively preserved light reflexes and, in some cases, absence of light-near dissociation. These findings differ from the pupillotonia of the Holmes-Adie syndrome. Barbara Wilhelm (Tuebingen, Germany) presented the Pupillographic Sleepiness Test as an objective test of daytime sleepiness and suggested its potential application in evaluating sleep disorders, driver sleepiness, drug effects, hangovers, and in other chronobiologic studies.

MAGNETIC RESONANCE IMAGING

Sofia Eriksson (Goteborg, Sweden) discussed new investigational studies using diffusion tractography to depict white matter signal abnormalities within the brain, showing its application in planning surgical resection of intracranial tumors and evaluating cortical heterotopias. Catherine Bennett (Leicester, England) examined functional MRI in patients confronted with a "filling in" stimulus. They demonstrated a cortical region of activation consistent with the presentation of a central stimulus, supporting the theory that "filling in" is an active process. Natalia Eliseeva (Moscow, Russia) used high resolution coronal MR imaging to examine the optic nerve and subarachnoid space diameter in patients with papilledema. They found that papilledema was associated with a wider mean diameter of the subarachnoid space. More interestingly, they also found that the size of the optic nerve was increased in patients with moderate degrees of papilledema and decreased in severe or atrophic papilledema. Simon Hickman detected enhancement of the optic nerve in 27 of 28 patients with acute optic neuritis using serial gadolinium-enhanced, fat-saturated, T1-weighted spin echo MRI images. The median duration of enhancement was 63 days. Detlef Kompf (Lubeck, Germany) used functional MRI to demonstrate a distinct representation of visually-guided eye and hand movements in the human posterior parietal cortex. The cortex lateral to the intraparietal sulcus predominantly controls saccadic movements, while the cortex medial to the intraparietal sulcus predominantly controls visually-guided reaching movements. Irene Notting (Leiden, The Netherlands) analyzed four cases of suprasellar germinoma and stated that diagnostic biopsy is warranted when a chiasmal mass resembling a glioma is associated with diabetes insipidus or other endocrinologic abnormalities and rapid visual decline (Figs. 4, 5).

MULTIPLE SCLEROSIS

Mats Sandström (Stockholm, Sweden) reviewed the natural history of multiple sclerosis and argued for early
and aggressive treatment in light of recent findings that demyelination is ongoing between clinical attacks. John Barbur investigated the recovery of visual and pupillary function in demyelinating optic neuritis and multiple sclerosis. He confirmed that afferent pupillary defects often remained despite significant improvement in vision, and that patients with recurrent demyelinating attacks showed a greater deficit in the “pupil color response” compared with the pupillary light reflex.

INTRACRANIAL DISORDERS
Mark Kupersmith, MD (New York, NY) provided an excellent overview of intracranial dural arteriovenous malformations, detailing current theories of pathogenesis, clinical presentation, pathophysiology, and management. Elizabeth Graham (London, England) described clinical findings, treatment, and prognosis of neuro-Behget’s disease based on her extensive series of 23 patients from The National Hospital. All patients had anterior segment inflammation. Optic atrophy was present in 12 patients, usually due to recurrent vascular occlusion. Sixteen of 18 patients with retinal vein occlusion developed permanent neurologic deficits, in contrast to none of four patients with isolated retinal infiltrates. Irene Gottlob (Leicester, England) used video-oculography to show that patients with schizophrenia have an abnormally high number of saccades and smaller saccadic amplitudes when reading. Discussants raised the question of whether these results could be cognitive in origin since other saccades are normal (although antisaccades are abnormal). Kristina Stenberg (Gothenburg, Sweden) described a patient who developed a combination of bilateral posterior ischemic optic neuropathy and bilateral internuclear ophthalmoplegia following lower spine surgery with spinal fusion. Mark Kupersmith described the natural history of idiopathic hypertrophic meningitis in 11 patients followed for a mean of 2.3 years. He pointed out that these patients are initially corticosteroid-responsive but that immunosuppressive agents are often necessary because
clinical manifestations can often recur when corticosteroids are tapered.

**PEDIATRIC NEURO-OPHTHALMOLOGY**

Michael Brodsky (Little Rock, AR) reviewed neurologic mechanisms of congenital strabismus and proposed in this condition the eyes revert to their ancestral function as physiologic vestibules which alter central vestibular tone in any of three planes. Helmut Wilhelm examined 37 patients with amblyopia and confirmed the existence of an afferent pupillary defect of up to 0.6 log units in the absence of organic disease. Michael Brodsky presented two patients who had infantile facial hemangioma and ipsilateral peripapillary excavation (morning glory disc anomaly in one case and peripapillary staphyloma in the other). In both cases, MR angiography showed ipsilateral carotid dysgenesis, suggesting that this association, which is found only in girls, falls within the PHACE syndrome (posterior fossa abnormalities, hemangioma, arterial anomalies, cardiac abnormalities, and eye anomalies). Lene Martin (Stockholm, Sweden) used Rarebit perimetry to document impaired visual function in 25 subjects who had intrauterine growth restriction. Although frequency doubling perimetry, visual acuity, and color vision were normal, eight patients had impaired visual function when tested with Rarebit perimetry, and also showed a reduced neuroretinal rim-to-disc ratio. Barbara Wilhelm presented evidence that children with attention deficit hyperactivity disorder may suffer from daytime sleepiness as measured by pupillography. In a patient with congenital sensory nystagmus from corneal dystrophy, I Choudhuri (Leicester, England) found that gabapentin 2400 mg/d improved visual acuity from 20/80 to 20/40 and reduced nystagmus intensity as measured by infrared videography (Fig. 6).

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University of Ark
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Daniel M. Jacobson, MD
(1956–2003)

On July 27, 2003, our friend and colleague Daniel M. Jacobson, 47, died peacefully in the Palliative Care Unit at St. Joseph's Hospital in Marshfield, Wisconsin. With his wife Ruth and his older daughter Taylor at his side, his long and often painful battle with cancer was over.

A Jewish memorial service was held on July 30, 2003, at the First Presbyterian Church in Marshfield with Rabbi Dan Danson officiating. Following the service, the internment was held at the Hillside Cemetery in Marshfield.

At the memorial service, Dan was remembered as a great friend to all. He was a devoted son to his parents and greatly admired by his brothers and sisters. He was a caring and loving husband to Ruth and a loving father to their three children, Taylor Ann, 15, Alex Elizabeth, 12, and Graeme Scott, 8, all born in Marshfield.

FIG. 1. Dan Jacobson

Dan was born in East Grand Rapids, Michigan, graduating from East Grand Rapids High School in 1974. He attended college at the University of Texas-Austin and medical school at the University of Texas-Houston. He received his neurologic training at the University of Pittsburgh, and his neuro-ophthalmological fellowship training at the University of Iowa under the direction of H. Stanley Thompson, MD, and James J. Corbett, MD. In 1987, he joined the staff of the Marshfield Clinic in the Departments of Neurosciences and Ophthalmology. He was appointed to the clinical faculty at the University of Wisconsin Medical School in 1988. At the Marshfield Clinic, he was the recipient of numerous teaching and research awards. He served on the Marshfield Clinic Research Committee starting in 1990, and as chairperson for seven years. He was widely known for his ability to bridge the gap between basic science and applied medicine. In 2001, he received the Gwen D. Sebold Research Fellowship Award, recognizing him as one of the outstanding researchers in the Marshfield Clinic system.

In the neuro-ophthalmic community, we knew him as a dedicated and compassionate physician. He excelled as a clinician and as a researcher. Dan always enjoyed being an active participant at the NANOS and Frank B. Walsh Society meetings. In his research, he tackled issues of great practical importance in the management of patients. Expertly designed and beautifully written, his works are among the most widely cited in our field. His lectures, based on painstaking review of the literature, were often the most definitive and most original "take" on the subject. Yet he was consistently humble about his achievements and complimentary about those of his colleagues. We will never forget his spirit.

The Dan Jacobson Chair of Neuro-Ophthalmology Memorial Fund has been established at the Marshfield Clinic Research Foundation to help carry on his legacy of empathic patient care, critical thinking, clear writing, and innovative teaching. Donations may be sent directly to the Marshfield Clinic Research Foundation, 1000 North Oak Avenue, Marshfield, WI 54449. For further information, contact Steve Yorde, Director of Resource Development, at (715) 389-3899.

Dennis R. Anderson, MD
Marshfield, Wisconsin

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Sadun Delivers First Jonathan Wirtschafter Visiting Professorship

One hundred and fifty family members, friends, and colleagues joined Jonathan Wirtschafter, MD, on August 29 and 30, 2003, to celebrate the inaugural Jonathan Wirtschafter Visiting Professorship in the Department of Ophthalmology at the University of Minnesota Medical School in Minneapolis. A reception, dinner, and testimonial to Dr. Wirtschafter’s professional and personal achievements took place on August 29th. The next day, a symposium took place, with case presentations followed by the visiting professor lecture. The lecture was given by Alfredo Sadun, MD, PhD, and was titled, “Leber Hereditary Optic Neuropathy: New Lessons from a Giant Pedigree in Brazil.” The day concluded with an open house hosted by Jonathan and Carol Wirtschafter. Individuals interested in contributing to the lectureship can contact the Vision Foundation, University of Minnesota, Department of Ophthalmology, MMC 493, 420 Delaware St SE, Minneapolis, MN 55455.

Howard D. Pomeranz, MD, PhD
Minneapolis, Minnesota

FIGURE 1. Jonathan D. Wirtschafter, MD (Minneapolis, MN), flanked on the left by Alfredo A. Sadun, MD, PhD (Los Angeles, CA), the first Jonathan Wirtschafter Visiting Professor, and on the right by Jack Barchas, MD, Chair, Department of Psychiatry, Weil Cornell Medical College, New York, NY.
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Upcoming Meetings

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

May 2–7, 2004
Association for Research in Vision & Ophthalmology Annual Meeting (ARVO)
Fort Lauderdale, Florida
http://www.arvo.org/Meetings/meetgrid.asp
Contact: arvo@arvo.org

February 5–7, 2004
International Stroke Conference
San Diego, California
http://www.strokeconference.org/portal/strokeconference/sc/
Contact: strokeconference@heart.org

May 12–14, 2004
13th European Stroke Conference
Mannheim-Heidelberg, Germany
Contact: Hennerici@eurostroke.org

March 27–31, 2004
American Association of Pediatric Ophthalmology & Strabismus Annual Meeting
Washington, DC
http://amed-aapos.bu.edu/
Contact: TSPPlanIt@aol.com

May 22–25, 2004
The Society of Neurological Surgeons 2004 Annual Meeting
Louisiana State University
New Orleans, Louisiana
http://www.societyNs.org/meeting/index.html

April 24–May 1, 2004
Renaissance Orlando Resort at Seaworld
Orlando, Florida
http://www.nanosweb.org/meetings/
Contact: (860) 586-7507

June 1–4, 2004
46th Annual Scientific Meeting of the American Headache Society
Philadelphia, Pennsylvania
http://www.ahsnet.com
Contact: ahsq@talley.com

April 25–30, 2004
56th Annual Meeting of the American Academy of Neurology (AAN)
San Francisco, California
http://www.aan.com/professionals/index.cfm
Contact: 651-695-1940, web@aan.com

June 5–11, 2004
42nd Annual Meeting of the American Society of Neuroradiology (ASNR)
Washington State Convention & Trade Center
Seattle, Washington
http://www.asnr.org/asnr/UpcomingMeetings.htm
Contact: 630-574-0220

May 1–6, 2004
Canadian Congress of Neurological Sciences Annual Meeting
Calgary, Alberta (Canada)
http://www.ccns.org
Contact: brains@ccns.org

June 8–12, 2004
5th World Stroke Congress
Vancouver, British Columbia (Canada)
http://www.kenes.com/stroke2004/
Contact: stroke2004@kenes.com

June 23–26, 2004
Canadian Congress of Neurological Sciences Annual Meeting
Calgary, Alberta (Canada)
http://www.ccns.org
Contact: brains@ccns.org
June 26–30, 2004
14th Meeting of the European Neurological Society
Barcelona, Spain
http://www.ensinfo.com/
Contact: gerard.said@bct.ap-hop-paris.fr

June 29–July 2, 2004
16th International Perimetric Society Meeting
Barcelona, Spain
http://webeye.ophth.uiowa.edu/ips/Meetings/Barcelona04.htm
Contact: ips2004@unicongress.com

July 18–22, 2004
International Neuro-Ophthalmology Society (INOS)
Geneva, Switzerland
http://www.symphorg.ch/inos
Contact: inos@symphorg.ch

September 4–7, 2004
8th European Federation of Neurological Societies
Congress
Paris, France
http://www.kenes.com/efns2004/
Contact: efns04@kenes.com

September 21–23, 2004
27th Annual Japan Neuroscience Meeting
Osaka International Convention Center (Grand CUBE Osaka)
Osaka, Japan
Contact: hhida@med.nagoya-cu.ac.jp

October 3–6, 2004
129th Annual Meeting of the American Neurological Association
Toronto, Ontario (Canada)
http://www.aneuroa.org/annual-meeting/menu.shtml
Contact: lorjanderson@msn.com

October 23–28, 2004
34th Annual Meeting of the Society for Neuroscience
San Diego, California
http://web2.sfn.org/content/Meetings_Events/FutureandPastAnnualMeetings/index.html
Contact: info@sfn.org

November 16–19, 2004
Annual Meeting of the American Academy of Ophthalmology (AAO)
New Orleans, Louisiana
http://www.aoa.org/annual_meeting/
Contact: meetings@aoa.org

March 18–21, 2005
XXVth Pan American Congress of Ophthalmology
Santiago, Chile
http://www.paaao.org/pau_cong.htm
Contact: info@paaao.org

November 5–11, 2005
XVIIIth World Congress of Neurology
Sydney, Australia
http://www.wcn2005.com
Contact: conference@wcn2005.com

Erratum
In the September 2003 issue, the reference for Figure 2 in the article titled “Pituitary Apoplexy Causing Optic Neuropathy and Horner Syndrome without Ophthalmoplegia” was attributed incorrectly. Figure 2 of this article was adapted with permission from the following: