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Defining the Spectrum of Lyme Disease: A Difficult Proposition

Andrew R. Pachner, MD

Chronic infections are notoriously difficult challenges for the clinician. With respect to determining their clinical spectra, diagnosing them, treating them, or studying their epidemiology, they are daunting. HIV, tuberculosis, syphilis, malaria, and Lyme disease, to name just a few, continue to vex us and make us humbler and wiser physicians.

The study by Sibony et al in this issue of *Journal of Neuro-Ophthalmology* (citation here) is an effort to determine whether various forms of optic neuropathy are within the spectrum of Lyme disease. The authors used a retrospective chart review of patients within a patient database at SUNY Stony Brook School of Medicine; the school is located in an area endemic for Lyme disease. Out of 440 patients presenting with optic neuritis, the authors found that only five (1%) had compelling evidence that active *Borrelia burgdorferi* was responsible for, or contributed to, their visual deficit. This would indicate that in an academic center in an endemic area in the United States, extremely few patients with optic neuritis had Lyme disease as a cause, and that it is not a common cause of optic neuritis.

Why did I include the qualifier “in the United States” in the aforementioned sentence? Because Lyme neuroborreliosis has different clinical phenotypes for different genotypes of infecting subtypes of *B. burgdorferi* spirochetes. This has been an observation in the human disease (1) and its animal models (2). Thus, the conclusions drawn from the study of Sibony et al may not be readily applicable to Lyme disease in Europe, where the disease has a more aggressive neurologic presentation (3). Not surprisingly, investigators in Europe such as the Finns (4) and the Germans (5), both appropriately quoted in the study of Sibony et al, might dispute the conclusion that optic neuritis is rare in Lyme neuroborreliosis. The difference is likely because of the fact that American neuroborreliosis is caused predominantly by *B. burgdorferi sensu stricto*, whereas European disease is caused by *B. garinii* or *B. afzelii*, and the genetic differences between these subspecies are considerable.

Another issue that the authors did not address is the nagging question of whether our serological assays (enzyme-linked immunosorbent assay and Western blot) are so powerful that they will always be positive in cases of optic neuritis caused by *B. burgdorferi*. My answer is, possibly not! The concern is that in this chronic infection, it is conceivable that spirochetes can be cleared from the periphery but retained in “immune-privileged” sites such as the eye or the brain. Thus, an enzyme-linked immunosorbent assay-positive but Western blot-negative patient with optic neuritis could conceivably be infected yet have a localized process without adequate peripheral activation to become Western blot positive. A similar situation occurs in tertiary neurosyphilis, in which the CSF (cerebrospinal fluid) VDRL can be negative in a substantial percentage of cases despite a positive serum FTA-ABS.

These remarks do not detract, of course, from a very nice contribution to the literature by Sibony et al, especially in pointing out that optic nerve involvement in Lyme borreliosis in...
the United States is predominantly found in the child with meningitis, increased intracranial pressure, and optic disc edema. Retrobulbar neuritis remains very unlikely to be caused by Lyme disease; most likely it has another cause.

REFERENCES
Are We Ready to Replace Cocaine With Apraclonidine in the Pharmacologic Diagnosis of Horner Syndrome?

Randy Kardon, MD, PhD

In this issue of the Journal of Neuro-Ophthalmology, Freedman and Brown have presented two cases of Horner syndrome, adding to their two previously reported series of six (1) and eight (2) cases in which the diagnosis of oculosympathetic defect was pharmacologically confirmed using topical 0.5% apraclonidine in place of cocaine. Thirty minutes after apraclonidine, the miotic eye with the oculosympathetic defect dilated and the anisocoria reversed in all but one patient.

As a result of these findings, the authors have proposed that apraclonidine be considered a viable alternative to cocaine for pharmacologic confirmation of Horner syndrome. If topical apraclonidine is found to be as sensitive and specific as cocaine in differentiating Horner syndrome from other causes of anisocoria, then it should replace cocaine, which is expensive, not readily available in most doctors’ offices, and, as a controlled substance, must be kept under lock and key.

Finally, apraclonidine has an advantage over cocaine in that it will actively dilate the affected eye and not the normal eye, making its action a positive (mydriatic) one in the affected eye rather than a negative one in the affected eye and a positive (mydriatic) one in the unaffected eye, as this is the case with cocaine testing.

As an alpha-2 adrenergic agonist, apraclonidine has been used to lower intraocular pressure after YAG laser treatment. Stimulation of the presynaptic alpha-2 receptor is thought to inhibit release of norepinephrine and reduce aqueous production. In one study (1), apraclonidine 1% had the same pressure-lowering effect in the affected eye of six patients with Horner syndrome as it did in the contralateral eye. During that study, the authors noticed an unexpected mydriatic effect in the eyes with Horner syndrome. This effect is attributed to the drug’s weak alpha-1 agonist property, which acts on the denervated, supersensitive iris dilator muscle. Apraclonidine did not appear to cause any significant effect on the pupil of the unaffected eye.

Unlike phenylephrine, whose corneal penetration varies widely among individuals, apraclonidine readily penetrates the cornea and gains access to the iris, so the limiting factor to its mydriatic effect is whether alpha-1 supersensitivity is present in the iris dilator muscle. As early as 1989, the mydriatic effect of topical clonidine in Horner syndrome patients was described in the German literature (3). Apraclonidine has potential advantages over phenylephrine not only in its ease of corneal penetration but also in the fact that it does not need to be diluted. The advantage of apraclonidine over alpha-1 mydriatics, like epinephrine and phenylephrine, used in the past to diagnose Horner syndrome, is that its alpha-1 activity is relatively weak and will not dilate the normal pupil. In a reasonably high concentration (0.5%), apraclonidine will penetrate the cornea and arrive at the alpha-1 receptors of the iris dilator muscle. Strong alpha-1 mydriatics like epinephrine and phenylephrine had to be...
diluted to the point at which they barely made it through the cornea, and this made them work for some people and not for others.

Should we make the switch from cocaine to apraclonidine? Before doing so, we need more rigorous data to help answer some critical questions. For example, we do not know whether all interruptions of sympathetic outflow cause alpha-1 supersensitivity at the iris dilator muscle, which is required for apraclonidine to have its mydriatic effect, and whether some normal eyes will dilate when exposed to apraclonidine. Also, we do not know how long it takes for significant supersensitivity to develop.

A major concern relates to whether all tumors or carotid dissections will cause supersensitivity at the end organ. And if so, how long does it take for enough supersensitivity to develop to allow apraclonidine to have a significant mydriatic effect? Cocaine will confirm an oculosympathetic defect as long as there is diminished release of catecholamine from any cause at the iris neuromuscular junction in the affected eye. Unlike cocaine, apraclonidine depends on supersensitivity. If supersensitivity does not develop promptly, then theoretically apraclonidine may have a negligible mydriatic effect in the presence of a compressive lesion. In the 2003 case study by the authors (2), one patient out of eight had negligible apraclonidine reversal of anisocoria and had an oculosympathetic defect of unknown cause of 9 years’ duration. A second patient had only a small change in anisocoria after apraclonidine. In this patient, Horner syndrome had been present for 4 months. This was the only patient in the series with a compressive lesion (a cervical goiter). In another study quoted by the authors (4), supersensitivity to 1% phenylephrine was found in 10 (71%) of 14 patients with Horner syndrome. Four patients did not show significant mydriasis compared with normal controls.

In Loewenfeld’s encyclopedic text on the pupil (5), she indicates two mechanisms by which supersensitivity develops. In the first, there is loss of the ability to terminate the adrenergic response because of degeneration of the postganglionic neuron, which normally provides a presynaptic re-uptake mechanism. This creates an “apparent” supersensitivity caused by the prolonged action of any sympathomimetic agonist. In the second—and more important—mechanism, supersensitivity is caused by receptor up-regulation, also called “true” supersensitivity. Loewenfeld provides evidence that disuse or pharmacologic blockade of sympathetic impulses can result in true supersensitivity even without actual pre-ganglionic or post-ganglionic nerve fiber loss. One would thus expect apraclonidine to cause mydriasis in compressive lesions, providing that the decrease in sympathetic firing is severe enough and of long enough duration.

The preliminary results of apraclonidine testing for Horner syndrome appear promising in this context. I recently administered the test to two patients with Horner syndrome caused by compressive lesions and monitored their responses using infrared videography and computerized pupillometry. The reversal of anisocoria was unequivocal, making me cautiously optimistic about the applicability of this agent in the diagnosis of Horner syndrome. We must now perform pharmacologic testing of a larger number of patients with anisocoria caused by Horner syndrome and other causes (including physiologic) in different age groups, using apraclonidine on 1 day and cocaine 1 week later. Such a study would help answer concerns about the sensitivity and specificity of apraclonidine in diagnosing oculosympathetic defects compared with the previous gold standard of cocaine testing (6).

Freedman and Brown and their colleagues in Lubbock deserve great credit for bringing this potentially useful effect of apraclonidine to the attention of the medical community. Such a study should also include pediatric patients, since apraclonidine has also been recently reported in the diagnosis of childhood Horner syndrome (7).

REFERENCES

Reactive Lyme Serology in Optic Neuritis

Patrick Sibony, MD, John Halperin, MD, P. K. Coyle, MD, and Kartik Patel, DO

Background: Establishing a causal relationship between optic neuritis and Lyme disease (LD) has been hampered by technical limitations in serologic diagnosis of LD. Even so, there is a general impression that optic neuritis is a common manifestation of LD.

Methods: Retrospective case analysis of Lyme serology in 440 patients with optic neuritis examined between 1993 and 2003 in a single neuro-ophthalmic practice at Stony Brook University Medical Center, Suffolk County, New York, a region hyper-endemic for LD.

Results: Lyme enzyme-linked immunosorbent assay (ELISA) was positive in 28 (6.4%) patients with optic neuritis, three of whom had syphilis with cross-reactive antibodies. Among the remaining 25 ELISA-positive patients, optic neuritis could be confidently attributed to LD in only one case, a patient with papillitis. The other 24 cases had reactive Lyme serologies related to a history of LD years earlier, asymptomatic exposure, false-positive results, or non-specific humoral expansion. The ELISA in these 24 cases were weakly positive and the Western blots were negative by Centers for Disease Control criteria. There were no significant clinical differences between the 25 seropositive optic neuritis cases and 50 seronegative optic neuritis cases.

Conclusions: Based on these cases and a review of the literature, there is insufficient evidence for a causal link between LD and retrobulbar optic neuritis or neuroretinitis. There is sufficient evidence to establish a causal link between LD and papillitis and posterior uveitis.

without posterior vitreous cells. We encountered five cases with bilateral disc edema, with relatively normal vision and intracranial hypertension caused by LD meningitis. We considered them separately as papilledema.

Anti-\textit{B. burgdorferi} antibodies were measured by ELISA and Western blot performed in the Clinical Immunology Laboratory at University Hospital, Stony Brook. The ELISA result, expressed as optical density (OD), was considered positive if it exceeded the mean OD of a seronegative control panel by \( \geq 3.0 \) standard deviations (negative cutoff). We expressed serum Lyme ELISA as the ratio of the patient's OD to the negative cutoff; a ratio \( \geq 1 \) was considered positive. Western blots were interpreted based on Centers for Disease Control (CDC) criteria (15,16). IgM blots were considered positive if at least two of the following three bands were present: 23, 39, or 41 kD, and developed within 1 month of the onset of vision loss. IgG blots were considered positive if at least five of the following 10 bands were present: 18, 23, 28, 30, 39, 41, 45, 58, 66, or 93 kD. Cerebrospinal fluid (CSF) was examined for local production of anti-\textit{B. burgdorferi} antibodies, with correction for CSF and serum immunoglobulin concentration. A CSF-to-serum Lyme antibody index of \( \geq 1.0 \) was considered indicative of intrathecal antibody production (17–19).

**Criteria to Establish Causation**

To assess whether optic neuritis was caused by LD in our cases and in the published literature, we incorporated surveillance criteria used by the Centers for Disease Control (15,16). This approach is similar to one previously described by Halperin et al (19) to evaluate the central nervous system manifestations of LD.

Category I. Definitive proof requires culture or histologic demonstration of \textit{B. burgdorferi} in the CSF or optic nerve of a patient with active LD and optic neuritis.

Category II. Strong evidence requires the following core elements: optic neuritis, endemic exposure, negative Venereal Disease Research Laboratory Slide Test (VDRL) or Rapid Plasma Reagin (RPR), exclusion of definite multiple sclerosis (MS) by Poser criteria (20), and a positive serum Lyme titer (ELISA or Indirect Fluorescent Antibody [IFA]), in association with at least one of the following: (a) encephalitis or meningitis with CSF pleocytosis, intrathecal antibody production, or CSF polymerase chain reaction (PCR) positive for \textit{B. burgdorferi} DNA, and a positive Western blot; (b) recent signs of LD, such as facial nerve palsy, arthritis, or radiculoneuritis, with positive serum ELISA confirmed by Western blot; and (c) recent physician-diagnosed EM, usually with flu-like symptoms.

Category III. Possible connection would include the core elements described and one of the following: (a) central nervous system involvement that does not meet grade IIa criteria (lack of a confirmatory positive Western blot or the absence of intrathecal antibodies); (b) compelling clinical signs of LD without a positive Western blot or documented syphilis serologies (this group would include cases of "possible EM" that was not physician-diagnosed); and (c) seropositivity by ELISA and Western blot without symptoms or signs of LD.

Category IV. Causal linkage is unlikely because the serological or clinical evidence is lacking (IVa) or an alternative diagnosis such as MS or syphilis is more likely (IVb).

Category V. There is insufficient information on the optic neuropathy or the diagnosis of LD.

**RESULTS**

Among the 440 cases with optic neuritis in whom serological tests for LD were available, 28 (6.4\%) cases had reactive Lyme serologies by ELISA. Three of the 28 had papillitis with cross-reactive antibodies because of syphilis (cases 26–28). Among the 25 remaining cases, 20 (80\%) had retrobulbar neuritis, 4 (16\%) had papillitis, and 1 (4\%) had bilateral neuroretinitis. There were 5 cases with papilledema caused by LD meningitis (cases 29–33). The clinical and serological findings on all cases are summarized in Table 1.

No cases with retrobulbar neuritis or neuroretinitis met criteria for category I ("definitive proof") or category II ("strong evidence") of a causal link to LD. One case with bilateral papillitis (Case 1) and a very high Lyme ELISA ratio met category II evidence for a causal link to LD.

Two patients with retrobulbar neuritis (Cases 2 and 3) who met category III criteria had a history of LD treated 9 to 13 years before the onset of optic neuritis. Although their ELISA were positive (Fig. 1) when they presented with optic neuritis, their Western blots were negative. Optic neuritis developed many years after antibiotic treatment (in one case with IV ceftriaxone) and vision improved before they were retreated with antibiotics. Neither had other signs of LD at the time optic neuritis developed.

Twelve cases (Cases 4–15) met category IVa ("causal linkage unlikely because serological or clinical evidence is lacking"), all with negative Western blots. None had a history of EM, facial nerve palsy, radiculoneuritis, or arthritis. One case (Case 12) had a questionable history of a tick bite followed by arthralgias that had resolved without treatment 7 years earlier. Another case (Case 8) had four IgG bands on Western blot, had worked outdoors, and had a history of back pains and periodontal disease. Among
TABLE 1. Clinical and serologic features of Lyme titer-positive patients with idiopathic optic neuritis, syphilitic optic neuritis, and Lyme meningitis with papilledema

<table>
<thead>
<tr>
<th>Case</th>
<th>Category</th>
<th>Age/gender</th>
<th>Optic neuropathy</th>
<th>Associated history or clinical findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>II</td>
<td>76/M</td>
<td>Papillitis (OU)</td>
<td>Headaches, confusion, rapid vision loss (20/200 OU), amaurotic pupils and disc edema OU; Improved on IV ceftriaxone; CSF PCR positive for Lyme 2 y prior: EM, treated with doxycycline</td>
</tr>
<tr>
<td>2</td>
<td>III</td>
<td>52/F</td>
<td>Retrobulbar</td>
<td>13 y prior: tick bite, EM; doxycycline, then iv ceftriaxone</td>
</tr>
<tr>
<td>3</td>
<td>III</td>
<td>35/F</td>
<td>Retrobulbar</td>
<td>9 y prior: flu, arthritis, + Lyme titer; doxycycline, resolved</td>
</tr>
<tr>
<td>4</td>
<td>IVa</td>
<td>40/F</td>
<td>Retrobulbar</td>
<td>2 y later: recurrent optic neuritis</td>
</tr>
<tr>
<td>5</td>
<td>IVa</td>
<td>21/F</td>
<td>Retrobulbar</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>IVa</td>
<td>42/F</td>
<td>Retrobulbar</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>IVa</td>
<td>46/F</td>
<td>Retrobulbar</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>IVa</td>
<td>27/M</td>
<td>Retrobulbar</td>
<td>Outdoor worker, back pains, periodontal disease</td>
</tr>
<tr>
<td>9</td>
<td>IVa</td>
<td>43/F</td>
<td>Retrobulbar</td>
<td>Periodontal disease</td>
</tr>
<tr>
<td>10</td>
<td>IVa</td>
<td>46/M</td>
<td>Neuroretinitis (OU)</td>
<td>Antecedent viral syndrome, Bartonella titer (1:1024)</td>
</tr>
<tr>
<td>11</td>
<td>IVa</td>
<td>14/M</td>
<td>Papillitis (OU)</td>
<td>Antecedent viral syndrome</td>
</tr>
<tr>
<td>12</td>
<td>IVa</td>
<td>67/M</td>
<td>Retrobulbar</td>
<td>8m later: recurrence OS; 7 y prior: ? Tick bite and arthralgias. no rx</td>
</tr>
<tr>
<td>13</td>
<td>IVa</td>
<td>66/M</td>
<td>Papillitis</td>
<td>Periodontal disease</td>
</tr>
<tr>
<td>14</td>
<td>IVa</td>
<td>18/F</td>
<td>Retrobulbar</td>
<td>Antecedent pharyngitis, + Monospot</td>
</tr>
<tr>
<td>15</td>
<td>IVa</td>
<td>47/F</td>
<td>Retrobulbar</td>
<td>Bilateral sequential optic neuritis</td>
</tr>
<tr>
<td>16</td>
<td>IVb</td>
<td>18/F</td>
<td>Retrobulbar</td>
<td>Definite MS**</td>
</tr>
<tr>
<td>17</td>
<td>IVb</td>
<td>23/M</td>
<td>Retrobulbar</td>
<td>Definite MS</td>
</tr>
<tr>
<td>18</td>
<td>IVb</td>
<td>34/F</td>
<td>Retrobulbar</td>
<td>Definite MS; 7 y prior: ? EM, no rx, resolves</td>
</tr>
<tr>
<td>19</td>
<td>IVb</td>
<td>20/M</td>
<td>Retrobulbar</td>
<td>Definite MS</td>
</tr>
<tr>
<td>20</td>
<td>IVb</td>
<td>28/F</td>
<td>Retrobulbar</td>
<td>Definite MS</td>
</tr>
<tr>
<td>21</td>
<td>IVb</td>
<td>28/F</td>
<td>Papillitis</td>
<td>Definite MS</td>
</tr>
<tr>
<td>22</td>
<td>IVb</td>
<td>35/F</td>
<td>Retrobulbar (OU)</td>
<td>Definite MS</td>
</tr>
<tr>
<td>23</td>
<td>IVb</td>
<td>34/F</td>
<td>Retrobulbar</td>
<td>Definite MS</td>
</tr>
<tr>
<td>24</td>
<td>IVb</td>
<td>41/F</td>
<td>Retrobulbar</td>
<td>Definite MS</td>
</tr>
<tr>
<td>25</td>
<td>IVb</td>
<td>36/M</td>
<td>Retrobulbar</td>
<td>Definite MS</td>
</tr>
<tr>
<td>26</td>
<td>IVb</td>
<td>73/M</td>
<td>Papillitis (OU)</td>
<td>4 mo hx of progressive painless vision loss; bilateral central scotomas CSF VDRL 1:128</td>
</tr>
<tr>
<td>27</td>
<td>IVb</td>
<td>35/M</td>
<td>Papillitis</td>
<td>Gonorrhea, tonsillitis, genital lesions. Non-reactive CSF VDRL</td>
</tr>
<tr>
<td>28</td>
<td>IVb</td>
<td>46/M</td>
<td>Papillitis/Vitritis</td>
<td>Homosexual encounters. Non-reactive CSF VDRL</td>
</tr>
<tr>
<td>29</td>
<td>II</td>
<td>9/M</td>
<td>Optic disc edema (OU)</td>
<td>3 wk prior: flu-like illness, EM Headaches, diplopia, sixth cranial nerve palsy</td>
</tr>
<tr>
<td>30</td>
<td>II</td>
<td>7/M</td>
<td>Optic disc edema (OU)</td>
<td>1.5 mo prior: fatigue and blurry vision Headaches, diplopia, and sixth cranial nerve palsy</td>
</tr>
<tr>
<td>31</td>
<td>II</td>
<td>9/M</td>
<td>Optic disc edema (OU)</td>
<td>1 mo hx of horizontal diplopia and headaches; divergence paresis</td>
</tr>
<tr>
<td>32</td>
<td>II</td>
<td>6/M</td>
<td>Optic disc edema (OU)</td>
<td>2 mo prior: tick bite then arthralgias. Sixth cranial nerve palsy</td>
</tr>
<tr>
<td>33</td>
<td>II</td>
<td>11/F</td>
<td>Optic disc edema (OU)</td>
<td>Tick bite followed by headache, seventh cranial nerve palsy</td>
</tr>
</tbody>
</table>

Three cases with antecedent febrile syndromes (cases 10, 11, 14), Case 14 had pharyngitis with a positive Monospot and Case 10 had bilateral neuroretinitis with a positive Bartonella titer. Three cases (Cases 8, 9, 13) had a history of periodontal disease.

Ten cases (Cases 16–25) were categorized as IVb (“causal linkage unlikely because an alternative diagnosis is more likely”) because they met Poser criteria for definite MS (20). Despite relapsing neurologic events, none of the nine patients who underwent lumbar puncture had intrathecal production of anti-*B. burgdorferi* antibody. Only one case (Case 16) had a positive Western blot (5 IgG bands) but no suggestive symptoms or signs of LD. One case (Case 25) who had 4 IgG bands on Western blot had
TABLE 1. (continued) Clinical and serologic features of Lyme titer-positive patients with idiopathic optic neuritis, syphilitic optic neuritis, and Lyme meningitis with papilledema

<table>
<thead>
<tr>
<th>Case</th>
<th>Category</th>
<th>Age/ gender</th>
<th>Lyme titer Ratio</th>
<th>Western blot (kD)</th>
<th>Serology</th>
<th>Spinal Tap</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>II</td>
<td>76/M</td>
<td>4.68</td>
<td>1gM: 23, 41, IgG: 18 23 28 39 41 45 58</td>
<td>nr, nr</td>
<td>199 398 2.49 120 + 1.03 WMH, ONE</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>III</td>
<td>52/F</td>
<td>1.13</td>
<td>IgM: neg, IgG: 23, 41 32 II</td>
<td>nr, —</td>
<td>56 2 — 0.46 WMH</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>III</td>
<td>35/F</td>
<td>1.51</td>
<td>IgM: 23, IgG: neg 32 II</td>
<td>nr, nr</td>
<td>28 28 0.15 + ONE</td>
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</tr>
<tr>
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<td>40/F</td>
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<td>WMH</td>
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<td>46/F</td>
<td>1.19</td>
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<td>24 2 0.12 — 0.42 ONE</td>
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<td>8</td>
<td>IVa</td>
<td>27/M</td>
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<td>IgM: 41, IgG: 28 41 45 93 33 II</td>
<td>nr, nr</td>
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<td>43/F</td>
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<td>WMH</td>
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<td>nr, nr</td>
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</tr>
<tr>
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<td>28/F</td>
<td>1.23</td>
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<td>nr, nr</td>
<td>WMH, ONE</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>IVa</td>
<td>35/F</td>
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<td>nr, —</td>
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<td>23</td>
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<td>34/F</td>
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<td>nr, —</td>
<td>35 29 0.37 + 1.32 WMH</td>
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<tr>
<td>24</td>
<td>IVa</td>
<td>41/F</td>
<td>2.29</td>
<td>IgM: neg, IgG: neg 33 II</td>
<td>nr, nr</td>
<td>81 10 0.06 — 0.80 WMH</td>
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<tr>
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<td>IVa</td>
<td>36/M</td>
<td>2.61</td>
<td>IgM: neg, IgG: 28 41 45 93 33 II</td>
<td>nr, nr</td>
<td>60 44 0.3 + 1.31 WMH</td>
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</tbody>
</table>

**Definite MS based on Poser diagnostic criteria (20).**

Category, level of evidence for causal link between optic neuropathy and LD; ON, optic neuritis; M, male; F, female; y, year; m, month; wk, weeks; EM, erythema migrans; nr, non-reactive; nd, not done; WMH, white matter hyperintensities on MRI; ONE, optic nerve enhancement on MRI; OCB, oligoclonal bands; OP, opening pressure.
Figure 1. Lyme ELISA serology ratio in patients who had idiopathic optic neuritis, syphilitic optic neuritis, or Lyme meningitis with secondary increase in intracranial pressure causing papilledema. A ratio of \( \geq 1 \) is considered positive. Note that Lyme ELISA ratios are normal or only mildly positive among patients with idiopathic optic neuritis (with one exception, case 1), higher in those with syphilitic optic neuritis (false-positives), and very high in those with Lyme meningitis and papilledema. Roman numerals indicate our criteria for strength of evidence of causal link between Lyme disease and optic neuritis. I, definite proof; II, strong evidence; III, possible; IV, unlikely.

A longstanding history of relapsing neurologic episodes that included brainstem and cerebellar signs at different times. He had been treated previously with intravenous ceftriaxone and never had arthritis, EM, facial nerve paresis, or radiculoneuritis. One case (Case 21) with papillitis had four IgG bands on Western blot with a 3-week episode of limb weakness and paresthesias 3 months before the onset of optic neuritis. These manifestations were followed 6 months later with new white matter lesions on brain MRI. One case (Case 23) had two IgM bands on Western Blot alone, but had a 13-year history of relapsing and progressive weakness, paresthesias, ataxia, and optic neuritis. Another case (Case 18) with definite MS had two IgM bands and three IgG bands on Western blot and a questionable history of LD based on the patient's description of an EM-like rash 7 years before the onset of optic neuritis. The remaining five patients with MS had Western blots that were unequivocally negative.

Three cases with papillitis (Cases 26–28) that had significantly elevated Lyme ELISA ratios met criteria for syphilis (Fig. 1). One case (Case 28) had an associated vitritis. All three had a positive VDRL and FTA. Only one case had CSF pleocytosis with a positive CSF VDRL. Lyme Western blots, performed in two cases, were negative.

Five cases with LD (4 boys, 1 girl, aged 6–11 years) had bilateral optic disc edema associated with meningitis and increased intracranial pressure (Cases 29–33). Each had normal acuity, pupils, and color vision and visual field enlargement of the blind spots. The optic disc edema was diagnosed as papilledema in these five cases. Four had headaches, four had diplopia caused by sixth cranial nerve palsy or divergence paresis, and one had a facial nerve palsy. Lyme ELISA ratios in each case were elevated between 6.75 and 9.70 (Fig. 1). Four of the five had undergone Western blot testing, three of whom were positive for both IgM (2–3 bands) and IgG (6–7 bands); one was positive for IgG (6 bands) alone. The case that did not have a Western blot performed had EM diagnosed by an experienced physician. Opening pressures on lumbar puncture ranged between 240 and 360 mm water, and cerebrospinal protein was elevated in two of four patients. Cerebrospinal fluid pleocytosis was present in all but one patient (16–48 cells/mm³); intrathecal antibody index was elevated in one patient. All symptoms and signs resolved after treatment with intravenous ceftriaxone; there were no recurrences.

Table 2 compares the demographic, clinical, and laboratory features of the 25 seropositive optic neuritis patients to 50 seronegative optic neuritis cases. There were no statistically significant differences between the two groups with respect to age, gender, eye involvement, follow-up, pain, visual acuities at presentation and follow-up, or the frequency of papillitis, MRI abnormalities, CSF abnormalities, and MS. Vision improved spontaneously or before initiation of antibiotic treatment of LD in 17 (68%) of the 25 seropositive cases.

DISCUSSION

Establishing a causal relationship between optic neuritis and LD requires a rigorous and restrictive analysis of the evidence (19,21–24). Despite a number of case reports claiming an association, strong evidence of a causal relationship has only been clearly established for papillitis (Table 3, and see Literature Review). Our experience, accumulated more than 10 years in a region hyper-endemic for LD, indicates that optic neuritis is an exceedingly uncommon manifestation of LD. During this time, we encountered only one case—a patient with papillitis—that could be confidently attributed to active *B. burgdorferi* infection. Notably, asymptomatic seropositivity to *B. burgdorferi* in an endemic region such as Suffolk County is 5% to 10%.
TABLE 2. Seropositive vs seronegative optic neuritis

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<tr>
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<th>Seropositive optic neuritis</th>
<th>Seronegative optic neuritis</th>
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<tbody>
<tr>
<td>Patients</td>
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<td>50</td>
</tr>
<tr>
<td>Eyes</td>
<td>29</td>
<td>51</td>
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Demographics

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<td>Gender</td>
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<td>Female</td>
<td>16</td>
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<tr>
<td>OS</td>
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Follow-up (months)

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<td>SD</td>
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Clinical features

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<td>42</td>
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<td>Visual acuity</td>
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<tr>
<td>At presentation</td>
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<tr>
<td>20/40 or better</td>
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<td>14</td>
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<tr>
<td>20/50 – 20/100</td>
<td>6</td>
<td>15</td>
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<tr>
<td>20/200 or worse</td>
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<td>22</td>
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<tr>
<td>At follow-up</td>
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<td></td>
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<tr>
<td>20/40 or better</td>
<td>25</td>
<td>43</td>
</tr>
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<td>20/50–20/100</td>
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<td>20/200 or worse</td>
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<td>Optic disc</td>
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<td>MRI</td>
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<tr>
<td>n =</td>
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<td>47</td>
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<td>n =</td>
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Continuous variables: 2-sample t test.
Categorical data: Fisher exact test.
ns, not significant; SD, standard deviation.
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<th>II (Strong)</th>
<th>III (Possible)</th>
<th>IV (Unlikely)</th>
<th>V (Insufficient information)</th>
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<td>Jacobson DM, 1989</td>
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<td>Lesser RL, 1990</td>
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<td>Kan L, 1998</td>
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<td>Rothermel H, 2001</td>
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<tr>
<td>Present study</td>
<td>29–33</td>
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| **Papillitis**                |                |             |               |               |                            |
| Wu G, 1986                   | 1^c            |             |               |               |                            |
| Schechter S, 1986            | 1^b            |             |               |               |                            |
| Farris BK et al, 1988        | 1^a            |             |               |               |                            |
| Gustafson R, 1988            |                | 1           |               |               |                            |
| Arnold RW, 1993              |                |             |               |               |                            |
| Bouat et al, 1995            | 1^b            |             |               |               |                            |
| Fedorowski JJ, 1996          |                |             |               |               |                            |
| Morales et al, 2000          | 1^a            |             |               |               |                            |
| Rothermel H et al, 2001      |                |             |               |               |                            |
| Present study                | 1              |             |               |               |                            |

| **Neuroretinitis**            |                |             | 11, 13, 21    | 26–28         |                            |
| Bialasiewicz et al, 1989     | 1^d            |             |               |               |                            |
| Winterkorn JMS, 1990         |                |             |               |               |                            |
| Lesser RL, 1990              | 1              |             |               |               |                            |
| Schoneherr U, 1991           |                |             |               |               |                            |
| Smith JL, 1991               |                |             |               |               |                            |
| Lesser RL, 1998              |                |             |               |               |                            |
| Lochhead J et al, 2001       | 1^a            |             |               |               |                            |
| Present study                | 10             |             |               |               |                            |

| **Retrobulbar optic neuritis**|                |             | 2,3, 4–9, 12, 14–20, 22–25 | 4          |                            |
| Lesser RL et al, 1990        | 2,3, 5         |             |               |               |                            |
| Strominger et al, 1994       |                |             |               |               |                            |
| Scott IU et al, 1997         |                |             |               |               |                            |
| Present study                | 2,3            |             |               |               |                            |

| **Ischemic optic neuropathy**|                |             | 4             |               |                            |
| Winward KE, 1989             |                |             |               |               |                            |
| Pizzarello LD, 1989          |                |             |               |               |                            |

| **Optic atrophy**            |                |             |              | 1             |                            |
| Winward KE, 1989             |                |             | 3             | 1             |                            |
| Bertuch AW, 1988             |                |             | 2             | 2             |                            |
| Morales et al, 2000          |                |             |               |               |                            |

The entry in each cell is the author's case number, categorized based on the definitions described in the methods section of this article. If the author's terminology differed from the category used in this Table or if the case did not clearly fall into a specific group, the superscript indicates an alternative categorical description, e.g., 'papillitis with intracranial hypertension'; ischemic optic neuropathy; neuroretinitis; uveitic papillitis. Papillitis cases 26–28 from the present study were caused by syphilis.

The positive serology does not differentiate between active infection and previous exposure. Patients may remain seropositive for years, even after adequate antibiotic treatment (16,27,28). This probably explains the two category III cases (Cases 2 and 3) and possibly two category IV cases (Cases 12 and 18) in subjects who may have had LD 7 to 13 years before optic neuritis developed. The remote history of LD, the absence of any coexistent signs of recurrent infection, the negative Western blots at the time of vision loss, and visual improvement without antibiotic
treatment suggest that the optic neuritis was probably unrelated.

False-positive Lyme serologies can occur in patients with other spirochetal infections (syphilis, periodontal disease, and relapsing fever) (29-32). This was evident in three of our cases with syphilis (Cases 26-28) who had quite elevated ELISA ratios (>5.00). Three seropositive category IVA patients (cases 8, 9, 13) had a history of periodontal disease. Serum Lyme ELISA may also be non-specifically elevated in patients with autoimmune diseases and other infections (33,34). Three of the category IVA cases (Cases 10, 11, 14) had false-positive Lyme serologies caused by previous exposure or non-specific humoral expansion from an unrelated viral or bacterial infection.

Lyme-seropositive optic neuritis in a patient with MS is often incorrectly attributed to Lyme disease. To qualify for a diagnosis of Lyme disease, such patients, who generally have longstanding and persistent immune CSF abnormalities, should have evidence of a specific CSF immune response to B. burgdorferi (35-39). Because none of our 10 patients with MS (Cases 16-25) had evidence of intrathecal production of anti-B. burgdorferi antibody or a clinical history compatible with LD, we believe that a causal relationship to LD is unlikely. Although case 16 had a positive Western blot, there were no other manifestations of LD and vision recovered before antibiotic treatment was instituted. The reactive Lyme serology in this patient presumably reflected a previous unrelated exposure.

Whereas the Western blot has eliminated many of the difficulties in the interpretation of the ELISA, it still has limitations. Although its specificity is high, its sensitivity is not. Interpretation is somewhat subjective and the procedure lacks standardization across laboratories. IgM criteria are only considered meaningful in cases with acute disease (16,19,33,34,40,41). Cases with non-Lyme spirochetal infections may have false-positive Western blots (31,33,34).

Nonetheless, we found the Western blot useful to confirm neurologic LD with optic neuritis. Blots were positive in the only category II patient (Case 1) with papillitis and in all four patients (Cases 30-33) with papilledema in whom the Western blot test was performed. Each of these had ELISA ratios of more than 4.0 and positive Western blots that exceeded the minimum CDC requirements. In contrast, the two cases with syphilitic papillitis (Cases 27 and 28) in whom Western blots were obtained, and 18 of the remaining 24 optic neuritis patients, had ELISA ratios less than 3.00 and Western blots that were unequivocally negative (≤1 IgM band, ≤3.0 IgG bands). Among five remaining cases (Cases 8, 18, 21, 23, 25) with formally negative Western blots (2 IgM bands and longstanding neurologic disturbances or 4 IgG bands), four had MS (Cases 18, 21, 23, 25).

Literature Review

There are several reported cases of papillitis that appear to meet category II evidence for a causal link to LD. Burkhard (42) described a 59-year-old woman with EM, facial nerve palsy, lymphocytic meningitis, and “papilledema.” Although the lumbar puncture opening pressure was not reported, a central scotoma in one eye and an arcuate scotoma in the other were more typical of papillitis than papilledema. Similarly, Rothermel et al (43) described three compelling cases of unilateral and bilateral papillitis in children with high serum titers, positive Western blots with 8 to 10 IgG bands, and other signs of LD.

Several additional case reports of papillitis caused by LD fall short of category II requirements (44-49) because syphilis serologies were not reported (45, 48), serum titers were negative (49), or Western blot was either not reported (44,45,48) or did not meet CDC criteria (47,46). These category III cases, considered individually, would not be sufficient to establish a causal linkage, but taken as a whole, support the category II cases of papillitis.

Four previously reported cases had features of both papilledema and papillitis, characterized by rapid vision loss, bilateral optic disc edema, and intracranial pressures ranging between 240 to 570 mm (43,46,47,50). Some of these cases might be grouped with the papilledema-meningitis cases, but the rapidity and severity of vision loss was more typical of papillitis.

Among the nine published cases of retrobulbar neuritis reportedly caused by LD (51-54), none meets rigorous criteria for a causal link to LD. Jacobson (51) described four patients with typical retrobulbar optic neuritis and positive serological and CSF findings of LD. However, in a follow-up letter to the editor 12 years later (52), two of the original four patients ultimately had MS diagnosed, and another, in retrospect, was believed to have a questionable link of LD. Although the remaining case nearly satisfied category II criteria, the IgG Western blot (with 3 bands) does not meet CDC requirements. Apart from a history of tick exposure, the patient had no features suggesting LD.

Lesser (53) described three patients (his cases 2, 3, and 5) with painful retrobulbar optic neuropathies and significantly elevated Lyme titers. The clinical evidence for LD in his cases 3 and 5 is compelling. However, these cases predate the widespread use of the Western blot, syphilis serologies were not reported, the single patient who underwent a lumbar puncture only showed nonspecific spinal fluid abnormalities and vision loss developed despite antibiotic treatment.

Scott (54) reported a 10-year-old girl with arthralgias and unilateral painful retrobulbar optic neuropathy, chiasmal MRI enhancement, elevated Lyme IgG IFA of 1:512, and four bands on the IgG Western blot. Spinal fluid...
and intrathecal antibody assays were negative. The clinical manifestations did not improve after antibiotic treatment. This case is similar to three of our cases (Cases 8, 21, 25) who had 4 IgG bands on Western blot. MS developed in two of them (Cases 21, 25). It is likely that all three had been previously exposed to the Lyme spirochete and the optic neuritis was probably not caused by LD. Strominger and Slamovits (84) described a 55-year-old seronegative woman with subclinical retrobulbar optic neuropathy, chronic radiculoneuritis, a positive CSF PCR and T cell proliferation assay, and a Herxheimer reaction. However, this case does not meet the CDC criteria for the diagnosis of LD.

Based on the published literature, the causal link between neuroretinitis and LD has not been clearly established. Analysis is complicated by the varying clinical criteria used for diagnosis. Neuroretinitis (Leber's idiopathic stellate neuroretinitis) is strictly defined as a form of papillitis characterized by disc edema, stellate macular exudates, and posterior vitreous cells. The occurrence of non-inflammatory macular star with disc edema in severe papilledema, ischemic optic neuropathy, or acute hypertensive retinopathy, may be confused with neuroretinitis (55–58). Some authors have also applied the term neuroretinitis to any type of disc edema with uveitis or retinitis, even in the absence of a macular star (59–64), a condition we call “uveitis.”

The detection of B. burgdorferi DNA by PCR in the vitreous of a patient with pars planitis (65), the observation and culture of B. burgdorferi from intraocular specimens of patients with panuveitis (66), and its demonstration in the eye of an animal model with spirochetemia (67,68) all meet category I criteria and establish that B. burgdorferi can cause intraocular inflammation. Although neither we nor others (69,70) have seen cases of Lyme uveitis, these experimental studies, together with many reports on a variety of uveitic syndromes implicating LD (65,66,70–81), are sufficient to establish a plausible linkage between LD and uveitis (60,62,64,81–84).

The case for classically defined neuroretinitis is less clear. Our series included only one case of Lyme-seropositive neuroretinitis. The negative Western blot, the positive Bartonella titer, and the absence of any other clinical signs of LD make it unlikely that this patient had LD. Our case is similar to most of the other reported seropositive cases of neuroretinitis (2,6a,53,64,80,85). Although some had systemic prodrromes consisting of fatigue (80), arthralgias (53,80) fever (2,85), or mild CSF pleocytosis (79), these findings cannot be used to support a diagnosis of LD because such findings are common in patients with neuroretinitis. Reactive Lyme serologies in these cases may represent previous exposure or a virus-related humoral expansion.

One case (50) meets category III criteria for a neuroretinitis link to LD, that of a 7-year-old with a facial nerve palsy, followed 5 weeks later by acute vision loss, meningeal symptoms, bilateral disc edema, and “macular exudates” (but no posterior vitreous cells). The case had elements of both papillitis and papilledema, with intracranial pressure of 400 mm H2O, acellular CSF, positive serum and CSF Lyme antibody tests, and a positive CSF Lyme PCR. Western blot testing was not reported. This case unquestionably had LD but it was unclear if the macular exudates were the result of classic neuroretinitis or severe papilledema.

Some published cases that describe the ophthalmic manifestations of LD have omitted serological testing for syphilis (53,86,87). In others, serological testing indicated that syphilis was at least as likely to be the cause of the optic neuropathy (88,89). Our three cases of luetic papillitis underscore the importance of obtaining syphilis serologies in cases with optic neuropathies and reactive Lyme serologies. Because spirochetes share common antigens, serological tests frequently cross-react. Depending on the method, Lyme ELISAs may be positive in approximately 20% to 60% of cases with syphilis, whereas 20% of cases with LD may have a weakly positive FTA-ABS (usually <1:10). Reaginic tests, such as the RPR or VDRL, are usually negative in LD (31,90,91).

In contrast to most of our cases with optic neuritis, the five cases with papilledema consistently met category II evidence of a causal link to LD, with very high Lyme ELISAs, positive Western blots, or a physician-diagnosed EM (29). Among seven previously published case reports that provided detailed eye findings, four cases (43,92,93) meet category II criteria and three cases (53,94,95) meet category III criteria. In addition, at least five published series described “papilledema” in patients with neuroborreliosis, (96–100), although these reports did not always provide the opening pressure or the specifics about the eye findings. In some reported cases of LD with intracranial hypertension, the CSF protein concentration and cell count were normal, presumably because the spinal tap was performed either before or after a transient pleocytosis (53,92). In two cases (92) with initially normal CSF, lumbar puncture was repeated and demonstrated a pleocytosis in one case and elevated protein in the other. This may explain why some LD patients have a “pseudotumor-like” syndrome (53). The occurrence of papilledema in patients with Lyme meningitis is well-established and consistent with our experience.

In summary, there seems little doubt that LD can affect the optic nerve. The most common manifestation occurs in children with early disseminated disease: Lyme meningitis, intracranial hypertension, and papilledema. These patients have high serum Lyme ratios and unequivocally positive Western blots. Optic neuritis in LD is rare and usually expressed as a unilateral or bilateral papillitis.
during the early disseminated stage. Optic disc edema in posterior uveitis can also be caused by LD, although we have encountered this clinical presentation in only one patient with syphilis with a false-positive Lyme titer. There is no convincing evidence that LD causes retrobulbar neuritis. Although there is suggestive evidence (51,53,54) that a painless retrobulbar optic neuropathy may occur in chronic neuroborreliosis, this requires further confirmation. LD may ultimately be shown to cause classic neuroretinitis but compelling evidence of a causal linkage is lacking. Nonetheless, the workup for neuroretinitis should include testing for LD, particularly if there are signs of intraocular inflammation.

Optic neuropathy in LD does not generally occur in isolation; it is usually accompanied by meningeval symptoms, antecedent febrile illness, EM, facial nerve palsy, or arthritis. Positive Lyme serology in patients with isolated retrobulbar optic neuritis in the absence of other signs, or in patients with otherwise typical MS, may be misleading.

Acknowledgment
The authors are particularly grateful to Marc G. Golightly, PhD, Director of the Clinical Immunology Laboratory at University Medical Center, Stony Brook, for his invaluable technical advice and support.

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Abstract: Topical cocaine is used to confirm the clinical diagnosis of ocular sympathetic denervation, or Horner Syndrome (HS). Cocaine blocks re-uptake of norepinephrine (NE) by sympathetic nerve terminals in the iris dilator muscle, transiently increasing its concentration in the synaptic junction. Norepinephrine activates $\alpha_2$ receptors in the iris dilator to cause pupil dilation. In HS, cocaine fails to dilate the affected pupil as much as the unaffected pupil, but its indirect action makes it a weak dilator, and the test can give equivocal results. Cocaine is also a controlled substance and therefore difficult to obtain. A practical and reliable alternative to cocaine is apraclonidine, an ocular hypotensive agent that has a weak direct action on $\alpha_2$ receptors and therefore minimal to no clinical effect on the pupils of normal eyes. Patients with HS have denervation supersensitivity of the $\alpha_2$ receptors in the iris stroma of the affected eye, making the pupil dilator responsive to apraclonidine. In patients with HS, reversal of anisocoria occurs after bilateral instillation of apraclonidine 1% or 0.5%. Two cases that demonstrate this effect are reported. Apraclonidine should be considered a candidate to replace cocaine in the pharmacologic diagnosis of HS if a gold-standard comparison study confirms these results.


Horner syndrome (HS) (1–3) is classically described as a triad of clinical signs arising from disruption of sympathetic innervation to the eye and ipsilateral face that causes miosis, upper lid ptosis, mild elevation of the lower lid, and anhidrosis of the facial skin. Confirmation of a suspected clinical diagnosis of HS is made by pharmacologic testing of the pupils with cocaine, which will fail to dilate the pupil of an affected eye.

Cocaine is an indirect sympathomimetic agent that binds to monoamine NE transport proteins (4) on the sympathetic nerve endings in the iris, causing decreased re-uptake of NE from the synaptic junctions. Norepinephrine stimulates $\alpha_1$ receptors on the iris dilator muscle, causing contraction and an increase in pupil diameter. With complete sympathetic disruption, no dilation occurs because there is no tonic release of NE.

A plausible alternative to cocaine in the diagnosis of HS is apraclonidine (Iopidine; Alcon, Fort Worth, TX), a direct $\alpha$-receptor agonist with strong $\alpha_2$ and weak $\alpha_1$ activity (5). In normal eyes, the $\alpha_2$ activity tends to down-regulate the production and release of NE. Patients with chronic reduction or elimination of NE in the synaptic junctions have denervation supersensitivity of the $\alpha_1$ receptors (6). When apraclonidine is applied to the eye, the up-regulated smooth muscle $\alpha_1$ receptors are directly activated by the medication, causing pupil dilation. The $\alpha_2$ receptors are also activated, but because there is little NE production and release, further inhibition does not decrease the pupil diameter.

We have reported the use of apraclonidine 1% (7) and 0.5% (8) to confirm the diagnosis of HS. In these studies, pupil diameters were first measured in bright and dim illumination to the nearest 0.5 mm using a pocket pupil card. Then apraclonidine was instilled, and the measurements were repeated 30 minutes later. Reversal of anisocoria occurred, that is, the HS pupil became larger than the normal pupil.

Here we report two additional HS cases confirmed with topical apraclonidine to show its practical applicability and to promote the development of a larger clinical trial.

CASE REPORTS

Case 1

A 37-year-old man underwent a cervical discectomy for a C6–C7 disk herniation. He noted left upper lid ptosis beginning 2 weeks after surgery. The patient was examined by one of us (KAF) 5 months later. The left upper lid had 2 mm of ptosis. Under ordinary indoor illumination, the right pupil measured 4.0 mm and the left pupil 3.0 mm; in dim light the right pupil measured 6.0 mm and the left pupil 4.0 mm with obvious dilation lag (Fig. 1A). Apraclonidine 0.5% was instilled into both eyes. Approximately 30 minutes later, reversal of anisocoria occurred with the right pupil dilating more than the left.
FIG. 1. Case 1. A 37-year-old man noted left upper lid ptosis 2 weeks after cervical disk surgery. This examination took place 5 months later. A. Before instillation of apraclonidine 0.5% in room light. Pupil OD measures 4.0 mm, pupil OS measures 3.0 mm. B. Thirty minutes after instillation of apraclonidine 0.5% in room light. Pupil OD measures 3.5 mm, pupil OS measures 5.0 mm. The anisocoria was been reversed. Note also the resolution of the left upper lid ptosis and left lower lid elevation.

Case 2
A 5-year-old boy was noted at birth to have unequal pupil size with the left pupil smaller and an obvious difference in iris color. There was no history of birth trauma or difficulty moving the left arm in infancy. All findings were stable and the child’s growth and development were normal. History regarding decreased sweating of the left forehead was unclear. The patient was referred to one of us (SMB) for a second opinion. Classic findings of congenital HS were present, including marked iris anisochromia (dark brown OD; light blue OS), anisocoria with the left pupil smaller (Fig. 2A), dilation lag of the left pupil, and increased anisocoria with reduced room illumination, left upper lid ptosis, and left lower lid elevation. After instillation of apraclonidine 0.5% into both eyes, the anisocoria reversed and the ptosis partially resolved (Fig. 2B).

DISCUSSION
Apraclonidine testing for HS is easily performed because this compound is a commercially available medication. The endpoint of testing is unequivocal and can be detected with the naked eye. Other clinical signs of denervation supersensitivity, such as resolution of ptosis, serve to increase the clinician’s confidence in the result.

We have previously reported the effect of apraclonidine in HS patients (7,8) using both the 1% (N = 6) and 0.5% (N = 8) concentrations. Eleven cases were pharmacologically confirmed with cocaine (N = 4) or...
hydroxyamphetamine (N = 7); of these, 10 showed reversal of anisocoria in response to apraclonidine, yielding a sensitivity of 0.91 for the apraclonidine test against these two customary agents.

The disadvantages of cocaine as a test agent for HS are many. Cocaine is a weak dilator of the pupil. In many instances, the normal (control) pupil will not dilate at all (9), raising doubts about the potency of the solution. Cocaine cannot diagnose a partial HS in which NE release is reduced but not eliminated; blocking reuptake may still cause pupil dilation. The drops sting when instilled. Because of its use as an illegal recreational drug, patients are often understandably wary of receiving cocaine in any form; urine metabolites are detectable after systemic absorption of ophthalmic solutions. Because it is a controlled substance, cocaine is difficult to obtain, and because of its short shelf-life, the solution must be compounded for each individual patient.

If apraclonidine does not cause reversal of anisocoria in a patient with strong clinical attributes of HS, the clinician may proceed to cocaine testing despite the practical difficulties. Because the apraclonidine test is primarily based on denervation supersensitivity, a false-negative result may occur in a very recently acquired HS because the α1 receptors have not yet up-regulated. Presumably in an acute complete HS, the cocaine test would more likely be positive.

The relatively low frequency of HS in the general population makes a more extensive study of the sensitivity and specificity of the apraclonidine test difficult. However, the increasing cost and difficulty associated with obtaining cocaine and hydroxyamphetamine might make a multicenter study worthwhile.

REFERENCES

The Visual Impact of Fractionated Stereotactic Conformal Radiotherapy on Seven Eyes With Optic Nerve Sheath Meningiomas

Monika Landert, MD, Brigitta G. Baumert, MD, PhD, Martina M. Bosch, MD, Urs M. Lüttolf, MD, and Klara Landau, MD

Background: Treatment of primary optic nerve sheath meningiomas (ONSMs) remains controversial. Although recent studies have suggested a favorable outcome of radiotherapy, controlled data on the efficacy of fractionated stereotactic conformal radiotherapy (SCRT) in primary ONSMs are still lacking.

Methods: Seven eyes treated with SCRT (total dose: 54 Gy) were compared with six eyes that were not treated because of patient or physician preference. The indication for intervention was deterioration of visual function with or without imaging evidence of tumor progression. Patients with secondary ONSMs and those with neurofibromatosis type 2 were excluded. The mean follow-up period was 57 months for the treated eyes and 61 months for the untreated eyes.

Results: Among the seven treated eyes, visual acuity improved in six, five of which sustained improvement of three or more Snellen lines. One eye deteriorated by two lines. Visual field improved in four eyes, remained stable in two, and deteriorated in one. Four untreated eyes showed worsening of visual acuity and two remained stable. Visual field deteriorated in three eyes and was stable in three. None of the untreated eyes experienced improvement in visual acuity or visual field. No complications of treatment were documented.

Conclusions: In agreement with previous reports, these results indicate that SCRT is superior to observation in its impact on visual function in eyes with primary ONSMs.

FIG. 1. Axial T1-weighted magnetic resonance imaging showing extent of presumed primary optic nerve sheath meningiomas in 12 study patients. Case 1, right orbital lesion. Case 2, bilateral orbitocranial lesions. Case 3, right intraorbital lesion. Case 4, right orbitocranial lesion. Case 5, right orbitocranial lesion. Case 6, right orbitocanicular lesion. Case 7, left orbitocanicular lesion. Case 8, right orbitocranial lesion. Case 9, left orbitocranial lesion. Case 10, right orbitocranial lesion. Case 11, left orbitocanicular lesion. Case 12, left orbital lesion.
TABLE 1. Clinical characteristics and outcomes in 7 treated and 6 untreated eyes with primary optic nerve sheath meningiomas

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Sex</th>
<th>Side affected</th>
<th>Treatment</th>
<th>Radiation dose (Gy)</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>44/F</td>
<td>OD</td>
<td>SCRT</td>
<td>$31 \times 1.7 = 52.7$</td>
<td>VA ↓, †</td>
</tr>
<tr>
<td>2</td>
<td>27/F</td>
<td>OD</td>
<td>SCRT</td>
<td>$30 \times 1.8 = 54.0$</td>
<td>VA ↓</td>
</tr>
<tr>
<td>3</td>
<td>50/F</td>
<td>OD</td>
<td>SCRT</td>
<td>$30 \times 1.8 = 54.0$</td>
<td>VA ↓</td>
</tr>
<tr>
<td>4</td>
<td>34/F</td>
<td>OD</td>
<td>SCRT</td>
<td>$28 \times 1.8 = 50.4$</td>
<td>VA ↓, †</td>
</tr>
<tr>
<td>5</td>
<td>59/F</td>
<td>OD</td>
<td>SCRT</td>
<td>$30 \times 1.8 = 54.0$</td>
<td>VA ↓</td>
</tr>
<tr>
<td>6</td>
<td>66/F</td>
<td>OD</td>
<td>SCRT</td>
<td>$30 \times 1.8 = 54.0$</td>
<td>VA ↓</td>
</tr>
<tr>
<td>7</td>
<td>46/M</td>
<td>OS</td>
<td>SCRT</td>
<td>$30 \times 1.8 = 54.0$</td>
<td>VA ↓, pain</td>
</tr>
<tr>
<td>Untreated group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>13/M</td>
<td>OD</td>
<td>None</td>
<td>—</td>
<td>RT refused</td>
</tr>
<tr>
<td>9</td>
<td>35/F</td>
<td>OS</td>
<td>None</td>
<td>—</td>
<td>RT refused</td>
</tr>
<tr>
<td>2</td>
<td>27/F</td>
<td>OS</td>
<td>None</td>
<td>—</td>
<td>VA and VF stable</td>
</tr>
<tr>
<td>10</td>
<td>76/F</td>
<td>OD</td>
<td>None</td>
<td>—</td>
<td>Only eye</td>
</tr>
<tr>
<td>11</td>
<td>33/F</td>
<td>OS</td>
<td>None</td>
<td>—</td>
<td>RT refused</td>
</tr>
<tr>
<td>12</td>
<td>53/F</td>
<td>OS</td>
<td>None</td>
<td>—</td>
<td>VA and VF stable</td>
</tr>
</tbody>
</table>

METHODS

Patient Selection

Only cases presenting clinically and radiologically with primary, rather than secondary, ONSM were included. Between 1989 and 2000, 18 cases were referred to the Department of Ophthalmology at the University Hospital of Zurich with the diagnosis of primary ONSM. Three patients were excluded because of previous surgical treatment, one because of neurofibromatosis type 2 with multiple meningiomas, and one because of previous conventional radiotherapy. One patient who received SCRT with no light perception before treatment was excluded because visual improvement after irradiation could not be expected.

Diagnosis was based on the clinical findings and the characteristic appearance on magnetic resonance imaging (20). The 12 cases included in the study had repeated magnetic resonance imaging studies, the last of which was performed at the end of the follow-up period. All cases had detailed orbital investigations using high spatial-resolution pre-contrast and post-contrast T1-weighted images with fat saturation, which allow improved visualization of meningiomas (21).

Thirteen eyes of twelve cases met entry criteria. Seven tumors were located on the right side and four on the left. One case had bilateral ONSM, one symptomatic, the other discovered incidentally with magnetic resonance imaging. Seven eyes were treated with SCRT (treated group). Six eyes were managed by observation only (untreated group). The single case with bilateral optic nerve sheath meningiomas was represented in both groups. Indications for treatment were deterioration of visual function with or without radiologically documented tumor growth. Untreated patients included three with satisfactory and stable visual function and three who did not wish to be irradiated despite progressive visual loss (Table 1). All treated patients gave informed consent before therapy. Our seven treated patients have been previously reported in a multicenter study published in a radiation oncology journal with emphasis on treatment technique and clinical outcome (5).

Patient Baseline Characteristics

There were 10 women (83%) and two men (17%). The female predominance prevailed in both treatment groups (Table 1). The mean age of the entire patient group at the time of presentation was 44.7 years (range: 13–76). Treated patients were older than untreated patients. The mean and median age in the treated group was 46.6 and 46 years, respectively; the mean and median age in the untreated group was 39.5 and 34 years, respectively.

In general, visual acuity at the time of diagnosis was better in the treated group than in the untreated group. All treated patients presented with 20/40 or better visual acuity immediately before treatment started. At initial presentation, half of the untreated eyes had a visual acuity ranging from 20/40 to 20/100, whereas the other half had normal vision.

Radiation Treatment

Seven cases were treated with highly focused irradiation in the form of fractionated SCRT at the Department of Radiation Oncology, University Hospital of Zurich. The
Optic Nerve Sheath Meningiomas


TABLE 1. (continued) Clinical characteristics and outcomes in 7 treated and 6 untreated eyes with primary optic nerve sheath meningiomas

<table>
<thead>
<tr>
<th>Case</th>
<th>VA before diagnosis</th>
<th>VA at diagnosis</th>
<th>VA 3 mo after RT</th>
<th>VA at 1 mo after RT</th>
<th>RT after diagnosis</th>
<th>Location/change</th>
<th>Imaging Location/change</th>
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<tr>
<td>1</td>
<td>20/32</td>
<td>20/40 @ 139</td>
<td>20/30</td>
<td>20/30</td>
<td>↑</td>
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<td>Intraorbital/stable</td>
</tr>
<tr>
<td>2</td>
<td>20/20</td>
<td>20/30 @ 62</td>
<td>20/20</td>
<td>20/20</td>
<td>↑</td>
<td>No change</td>
<td>Intraorbital/stable</td>
</tr>
<tr>
<td>3</td>
<td>20/20</td>
<td>20/30 @ 6</td>
<td>20/20</td>
<td>20/20</td>
<td>↑</td>
<td>No change</td>
<td>Intraorbital/stable</td>
</tr>
<tr>
<td>4</td>
<td>20/30</td>
<td>20/22</td>
<td>20/25 @ 36</td>
<td>20/25</td>
<td>↑</td>
<td>No change</td>
<td>Intraorbital/stable</td>
</tr>
<tr>
<td>5</td>
<td>20/25</td>
<td>20/25 @ 27</td>
<td>20/30</td>
<td>20/30</td>
<td>↑</td>
<td>No change</td>
<td>Intraorbital/stable</td>
</tr>
<tr>
<td>6</td>
<td>20/30</td>
<td>20/40 @ 4</td>
<td>20/25</td>
<td>20/25</td>
<td>↑</td>
<td>No change</td>
<td>Intraorbital/stable</td>
</tr>
<tr>
<td>7</td>
<td>20/25</td>
<td>20/30 @ 6</td>
<td>20/22</td>
<td>20/16</td>
<td>↑</td>
<td>No change</td>
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</tr>
<tr>
<td>8</td>
<td>20/70</td>
<td>HM @ 118</td>
<td></td>
<td></td>
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<td>Intracranial/stable</td>
</tr>
<tr>
<td>9</td>
<td>20/100</td>
<td>NLP @ 94</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>10</td>
<td>20/16</td>
<td>20/16 @ 87</td>
<td></td>
<td></td>
<td>↓</td>
<td>No change</td>
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</tr>
<tr>
<td>11</td>
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<tr>
<td>12</td>
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<td>HM @ 28</td>
<td></td>
<td></td>
<td>↓</td>
<td>No change</td>
<td>Intracranial/stable</td>
</tr>
<tr>
<td>13</td>
<td>20/16</td>
<td>20/16 @ 16</td>
<td></td>
<td></td>
<td>↓</td>
<td>No change</td>
<td>Intracranial/stable</td>
</tr>
</tbody>
</table>

Visual field (VF)

<table>
<thead>
<tr>
<th>Case</th>
<th>Visual field</th>
<th>Imaging Location/change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No change</td>
<td>Intraorbital/stable</td>
</tr>
<tr>
<td>2</td>
<td>+ 20°</td>
<td>Intraorbital/stable</td>
</tr>
<tr>
<td>3</td>
<td>No change</td>
<td>Intraorbital/stable</td>
</tr>
<tr>
<td>4</td>
<td>−9.0 dB</td>
<td>Intracranial/stable-regressive</td>
</tr>
<tr>
<td>5</td>
<td>+ 11.5 dB</td>
<td>Intracranial/stable</td>
</tr>
<tr>
<td>6</td>
<td>+ 70°</td>
<td>Intracanalicular/stable</td>
</tr>
<tr>
<td>7</td>
<td>−11.4 dB</td>
<td>Intracanalicular/stable</td>
</tr>
</tbody>
</table>

Visual field was considered as improved when expansion of at least 20° of the V-4-e isopter was recorded by Goldmann perimetry, or a decrease of at least 5 dB of mean deviation (MD) resulted on Octopus computerized perimetry. Therefore, +20° (Case # 2) indicates improvement on Goldmann perimetry, whereas −9.0 dB (Case # 4) indicates improvement on Octopus perimetry.

Main Outcome Measures

Baseline and follow-up assessments of visual acuity were performed by the same experienced neuro-ophtalmologist (K.L.). Best-corrected visual acuity was measured using Snellen charts and noted in a 20/20 ratio equivalent. At least three out of four letters had to be correctly identified for the patient to be given full credit for that line. If worse than 20/200, visual acuity was graded as counting fingers, hand motions, light perception, or no light perception.

In the treated group, visual acuity was recorded at 3 months after treatment in six of seven eyes and at the last follow-up visit (“final VA”) in all seven eyes. The visual field was tested either by Goldmann kinetic perimetry or by automated static perimetry with the Octopus program G2. A change in visual function was defined as change in visual acuity or visual field. A change in visual acuity...
consisted of improvement or worsening by two or more lines. A change in visual field consisted of an expansion or contraction of 20 degrees or more in the V-4-e isopter on Goldmann perimetry or a change of at least 5 dB in mean deviation (MD) on automated fields (22). The mean follow-up time was 57 months (range: 21–142) in the treated group, and 61 months (range: 16–118) in the untreated group. The mean follow-up time after radiotherapy in the treated group was 23 months (range: 8–40).

Statistical Analysis
Changes in visual function were classified as improvement, stabilization, or worsening. The treatment groups were compared with each other by the Mann–Whitney U test.

RESULTS
Visual Outcome
Among the seven treated eyes, six experienced improvement in visual function. Five eyes had an increase in visual acuity of three lines or more; one eye improved by one Snellen line. At 3 months after treatment, visual acuity had improved in five out of the six eyes in which it was recorded. One eye lost two lines of visual acuity. Visual field improved in four eyes, remained stable in two, and deteriorated in one.

Among the six untreated eyes, four showed moderate to severe worsening of vision. In three eyes with initial visual acuities ranging from 20/20 to 20/100, visual acuity declined to hand motion and no light perception, and one eye declined from 20/40 to 20/70. Two eyes with initially normal visual acuity maintained normal acuity over the follow-up period. Visual field deteriorated in three eyes and remained unchanged in three eyes.

Non-parametric statistical analysis revealed significantly better visual outcome for the treated group than the untreated group ($p = 0.012$).

Imaging Characteristics and Outcome
Three meningiomas were confined to the orbit, three involved the optic canal, and seven involved the intracranial space (Fig. 1). There was no difference in these patterns of involvement between the two groups (Table 1). Slight reduction in tumor size was noted in one treated patient. In the untreated group, one patient had enlargement of the tumor that extended both towards the globe and from the canal towards the chiasm. There were no long-term side effects of SCRT. One patient had acute eyelid edema and was treated with low-dose corticosteroids with subsequent symptom resolution.

DISCUSSION
The main finding in our series of 13 eyes with primary ONSM was a statistically significant improvement of visual function in the treated group as compared with the untreated group. Six of seven treated eyes (86%) experienced prompt improvement in visual acuity, visual field, or both. Five of those eyes (71%) had an increase in visual acuity of three lines or more and remained stable over a mean follow-up period of 23 months after SCRT. By contrast, three of six untreated eyes had profound visual loss.

Consistent with other series, our results show that stereotactic conformal radiotherapy in patients with progressive optic neuropathy caused by primary ONSM is superior to observation in preserving visual function. This improvement appears to be greater than found in previous studies. For example, the percentage of eyes with an improvement in visual acuity of at least three Snellen lines is higher than that reported by Pitz et al (14) and Narayan et al (12). Pitz et al (14) found functional improvement in 7 (44%) of 16 eyes (defined as improvement of visual acuity of two or more lines or change of at least 8% of visual field) over a mean follow-up period of 37 months, but only one eye (6%) gained more than two Snellen lines. Narayan et al (12) reported a three-line or greater visual acuity improvement in 5 (36%) of 14 patients treated with three-dimensional conformal radiation therapy with a mean observation time of 51.3 months.

The relatively low rate of visual improvement in these reports might be a reflection of an under-representation of eyes with pre-treatment mild or moderate visual loss. Our patients with marked improvement all had pretreatment visual acuities ranging from 20/40 to 20/30, which may allow a greater potential for good treatment results. Based on our interval visual acuity data, improvement in visual function appears to occur early after treatment initiation, resembling rapid visual recovery after surgical decompression in compressive optic neuropathy (23).

The number of eyes included in our study was small and our follow-up was short. Thus, no firm conclusions with regard to long-term risks of irradiation, visual preservation, or containment of tumor growth can be made. Our untreated group had worse baseline visual function than our treated group, so that conclusions about the beneficial effect of treatment must also be tempered.

Despite these weaknesses, our study supports the accumulating data on the efficacy of SCRT for primary ONSMs (4–6,10,14). We further confirm that without treatment, vision declines substantially in some cases (2,15,16,24) but remains stable in others (24). Our findings support SCRT for eyes with primary ONSM in which progression of optic neuropathy has been documented, but before severe visual loss occurs.
Acknowledgment

The authors thank Burkhardt Seifert, PhD, Department of Biostatistics, University of Zurich, Switzerland, for his expert statistical consultation.

REFERENCES

The Effects of Auditory Distraction on Visual Cognitive Performance in Multiple Sclerosis

Leonard L. LaPointe, PhD, Charles G. Maitland, MD, Adrienne A. Blanchard, MS, Brett E. Kemker, PhD, Julie A. G. Sitterwalt, PhD, and Gary R. Heald, PhD

Background: A subset of individuals with multiple sclerosis (MS) endures degradation of cognitive function during disease progression. The purpose of this study was to compare visual cognitive reaction time performance during three conditions of auditory distraction (four-talker babble; word repetition; babble combined with word repetition) to a quiet, undistracted condition.

Methods: Twenty-two patients with mild relapsing-remitting MS (Expanded Disability Status Scale mean of 3.0) and 17 age-matched and education-matched control subjects free of neurologic disease were tested on four cognitive visual processing subtests of simple reaction time, choice reaction time, and visual working memory for same and sequential digits concurrently during three conditions of auditory distraction.

Results: When reaction times for MS and control participants were pooled across all four cognitive tests, the scores of the MS patients in quiet (528 ms) were significantly slower than those of the control subjects (459 ms). The auditory distraction condition of word repetition combined with four-talker babble degraded cognitive performance more than most of the other distraction conditions in both groups.

Conclusions: Even in mild MS, subtle visual cognitive processing deficits may be elicited by auditory distraction.


An estimated 2,500,000 people in the world have multiple sclerosis (MS) and approximately 50% will have some form of cognitive dysfunction as a result of this disorder (1–4). Although cognitive dysfunction is more common among MS patients who have had the disease for a long time, little is known about the presence or severity of cognitive impairment in the early stages or in the milder severity levels of the disease. Behavioral concerns and reports on cognitive dysfunction in MS are supported by recent findings of brain atrophy in early MS (5,6).

The theoretical groundings of this research can be found in cognitive systems models of signal extraction from interference, competition, and distraction as outlined by Endsley (7) and by Rapp and Hendel (8). Further, the cognitive resource allocation model of Kahneman (9) offers explanatory power to studies of attention that have used divided attention and distraction paradigms to investigate cognitive degradation during interference. This model holds that a fixed cognitive resource capacity in humans requires either conscious or unconscious allocation of attention to competing stimuli. Therefore, if simultaneous cognitive task demands impinge on an array of human behaviors, some of these behaviors may be performed at less than optimal levels. Cognitive resource capacity can be allocated variably depending on levels of arousal, motivation, effort, task demands, and nervous system integrity. These theoretical concepts form the basis for the generation of our hypotheses regarding the effects of distraction on visual cognitive processing and performance in MS.

The purposes of this study are: (1) to determine the effects of different types of ecologically valid auditory distractions on visual processing and visual cognitive performance measures; and (2) to attempt to clarify the role of distractions on attention and cognitive resource allocation in MS.

METHODS

The MS group consisted of 22 patients (5 men, 17 women) with relapsing-remitting MS, ranging in age from 28 to 67 years (mean 49 years). Expanded Disability Status Scale (10) scores ranged from 0 to 4.5 (mean 3.0). The control group consisted of 17 subjects (8 men, 9 women) matched in age and education to the MS group, and ranging in age from 18 to 84 years (mean 48 years). No statistically...
Cognitive Measures

Four subtests from the California Computerized Assessment Package (11) were used to assess visual processing and visual cognitive function. This test measures reaction time and accuracy during the identification of visual stimuli precisely controlled in exposure duration time and interstimulus interval and presented on a 15-inch computer monitor. The subtests used for this study included:

1. Simple reaction time (“Press the space bar when you see any number on the screen.”)
2. Choice reaction time (“Press the space bar only when you see the number ’7′ on the screen.”)
3. Working memory, same number (“Press the space bar when you see two numbers in a row, e.g., ’5′ followed by ’5′.”)
4. Working memory, sequence (“Press the space bar when you see two numbers in incremental sequence, e.g., ’5′ followed by ’6′.”)

All participants had to pass a training sequence of trials to assure that they understood the instructions and were able to complete the computerized subtests. The four computerized subtests require approximately 8 to 10 minutes for completion.

Distraction Conditions

Three auditory distraction conditions were used for comparison of performance in the control quiet condition. These distraction conditions included:

1. Four-talker babble: four speakers (two men, two women) simultaneously read different passages of emotionally neutral informative material. This standardized auditory distraction material is contained on a CD and produced according to acoustically standardized conditions at AudrTec of St. Louis acoustic laboratories.
2. Word repetition: an examiner interjected words that the participant was asked to repeat. These words were taken from the Northwestern 6 word lists for testing auditory speech reception thresholds. Words were single syllable, phonetically balanced, and relatively frequently occurring in spoken English (eg, “fat,” “whip,” “goose”).
3. Combined four-talker babble with word repetition: a four-talker CD was played while the patients and subjects repeated words said by the examiner.

Before presentation of the distraction conditions, each participant’s hearing was screened. Auditory distraction levels were presented at 40 decibels (dB) above auditory threshold or 40 dB above the passed screening level of 25 dB. All distraction level conditions were presented concurrently during presentation of the cognitive tasks and were counterbalanced to distribute any order effect of learning or fatigue equally across all conditions. Examiners were not blinded as to whether participants belonged to the MS or control group.

Reaction times and accuracy scores were analyzed statistically using repeated measures between-group and within-group ANOVAs, with Bonferroni correction. Power analysis revealed an acceptable effect size for use of the statistical procedures selected for analysis.

RESULTS

Table 1 lists the results for both groups on each visual cognitive subtest in the quiet condition and in three distraction conditions.

When reaction times for MS and control participants were pooled across all four cognitive tests, the scores of the MS patients in quiet (528 ms) were significantly slower than those of the control subjects (459 ms). These differences reached significance for the pooled distraction conditions as well (MS = 551 ms versus controls = 483 ms; ANOVA F = 8.432, df = 1.38, P = 0.006).

When between-group differences across all visual cognitive subtests were analyzed across distraction conditions of quiet, four-speaker babble, word repetition, and

| TABLE 1. Reaction times (in ms) on visual cognitive subtests across quiet and distraction conditions for MS patients (N = 22) and control subjects (N = 17) |
|-----------------|-------|-------|-------|-------|-------|-------|-------|
|                 |       | Babble|       |       |       |       |       |
|                 | Control| MS    | Control| MS    | Control| MS    | Control| MS    |
| Simple          | 367 (65)*| 394 (65)| 345 (53)| 382 (67)| 419 (58)| 477 (108)| 401 (55)| 486 (162) |
| Choice          | 423 (45)*| 477 (66)| 421 (50)| 468 (60)| 455 (60)| 490 (73)| 458 (75)| 507 (98) |
| Same            | 507 (94)*| 601 (125)| 505 (107)| 581 (100)| 533 (124)| 607 (96)| 527 (107)| 621 (108) |
| Sequential      | 566 (115)*| 640 (119)| 578 (99)| 633 (105)| 602 (80)| 665 (96)| 596 (87)| 692 (128) |

*All numbers in parentheses refer to standard deviation.
word repetition and four-talker babble, MS performance was found to be significantly slower in all cases except for the easiest condition of simple reaction time in the quiet condition.

Among the distraction conditions, word repetition combined with four-speaker babble produced the slowest reaction times for both groups.

**DISCUSSION**

Our study found significant differences in reaction times for four visual processing and visual cognitive computerized subtests between MS patients and matched control subjects. This provides evidence to support the many previous studies that have found cognitive slowing or impairment in individuals with MS (1–4) but extends these findings to a sample of MS patients who are only mildly disabled by their MS (Expanded Disability Status Scale mean of 3.0). Additionally, the presence of auditory competition and distraction appears to add to the cognitive resource allocation load and diminish performance even more. We expect that these effects would be reciprocal across modalities and tasks. That is, we anticipate that visual distraction would affect auditory performance as well, a phenomenon yet to be elucidated. Distraction may be a means of taxing the cognitive system, particularly in the ability to efficiently allocate attentional resources that allows earlier detection of potential cognitive slowing. This suggests that evidence of impaired cognitive function may be a characteristic that is apparent early in the course of the disease progression if adequate measures of visual cognitive function are used, particularly within conditions of interference, competition, and distraction. We continue our investigation of longitudinal characteristics of decline and/or remission in MS, as well as our search for the distraction environments that differentially affect cognitive reaction time and accuracy.

**REFERENCES**

Ophthalmic Complications of Dental Anesthesia: Three New Cases

Josepha Horowitz, MD, Yehoshua Almog, MD, Alvit Wolf, MD, Gila Buckman, MD, and Orna Geyer, MD

Abstract: Two patients had ipsilateral optic neuropathy and one patient had an ipsilateral abduction deficit and a dilated, poorly reactive pupil immediately after anesthesia of upper alveolar teeth. In one patient with optic neuropathy, the optic disc was not swollen, brain and orbit computed tomography (CT) was negative, and vision recovered completely within 2 weeks. In the other patient with optic neuropathy, the optic disc was swollen, brain and orbit CT were negative, and vision did not recover. In the patient with ductional and pupil deficits, recovery was complete within 24 hours. Since 1960, 39 cases of ophthalmic complications have been reported in the English literature. A majority have followed anesthesia of upper alveolar teeth. In all but three cases, the deficits were temporary. Diffusion, inadvertent needle penetration into the orbit, venous injection, or retrograde arterial injection is postulated as the mechanism by which the anesthetic agent reaches the cavernous sinus or orbit to cause the deficits.


Ophthalmic complications of dental anesthesia are rare and almost always transient. They include ocular motor cranial nerve paresis, Horner syndrome, and visual loss. Symptoms generally develop immediately after injection of the anesthetic solution, persist no more than several hours, and are attributed to the anesthetic reaching the orbit or cavernous sinus. There are, however, a few reports of complications that cannot be attributed simply to the anesthetic effect, either because of delayed onset or persistent deficits (1–3). We present three new cases, two involving optic neuropathy, and one involving abduction paresis and mydriasis.

METHODS

The patients in this study were accrued by a detailed retrospective card review conducted on all patients evaluated on the neuro-ophthalmology service at the Carmel Medical Center, Haifa (JH) and the Sapir Medical Center, Kefar-Saba, Israel (YA) from January 2000 through December 2004. We tabulated details of the dental anesthesia and clinical manifestations. A Medline search was conducted for articles published in English from 1960 to the present using the following keywords: dental anesthesia and ocular, dental anesthesia and ophthalmoplegia, and dental anesthesia and visual complications.

CASE REPORTS

Case 1

A 30-year-old woman underwent tooth extraction from her right upper jaw because of a dento-alveolar abscess. After the procedure, she reported blurred vision in her OD. Ophthalmic examination a few hours later revealed visual acuity was 20/25 OD and 20/20 OS. A partial abduction deficit was present OD. Pupils measured 7 mm OD and 5 mm OS in dim light. The pupil OD reacted incompletely to direct light and a near target. There was no relative afferent pupillary defect, and the anterior segment, fundus, and visual fields were normal. Follow-up examination 1 day later showed no ophthalmic abnormalities.

Case 2

A 45-year-old healthy man noticed sudden visual loss in his OS 3 hours after root canal treatment in tooth 25 (left upper jaw). On examination 6 hours after the dental treatment, visual acuity was 20/20 OD and 20/100 OS. A partial abduction deficit was present OD. Pupils measured 7 mm OD and 5 mm OS in dim light. The pupil OD reacted incompletely to direct light and a near target. There was no relative afferent pupillary defect, and the anterior segment, fundus, and visual fields were normal. Follow-up examination 1 day later showed no ophthalmic abnormalities.

Case 3

A 45-year-old healthy man noticed sudden visual loss in his OS 3 hours after root canal treatment in tooth 25 (left upper jaw). On examination 6 hours after the dental treatment, visual acuity was 20/20 OD and 20/100 OS. There was a relative afferent pupil defect OS and color vision was impaired OS. Ophthalmoscopy revealed a small crowded disc OD and a pale swollen disc with flame shaped hemorrhages OS. Visual field OD was normal and demonstrated a lower altitudinal defect OS. A computed tomography scan of the brain and orbits was normal. A month later, visual acuity was unchanged and the optic disc OS was pale. One year later, the patient noticed sudden visual loss in his OD without provoking factors. Visual acuity was 20/80 OD and 20/100 OS. Ophthalmoscopy revealed a swollen disc with flame-shaped hemorrhages OD and a pale optic disc OS. Visual fields demonstrated lower altitudinal defects OU.

Carmel Medical Center (JH, AW, GB, OG), Haifa, Israel and Sapir Medical Center (YA), Kefar-Saba, Israel.

Address correspondence to Orna Geyer, MD, Head, Department of Ophthalmology Carmel Medical Center, 7 Michal Street Haifa, Israel; E-mail: drgo@netvision.net.il

<table>
<thead>
<tr>
<th>Reported cases</th>
<th>Patient age &amp; gender</th>
<th>Solution used for dental anesthesia</th>
<th>Clinical manifestations</th>
<th>Onset</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hales, 1970</td>
<td>16 M</td>
<td>Lidocaine 1% + adrenaline</td>
<td>Dizziness, dilated pupil</td>
<td>“Later that day”</td>
<td>Normal exam 4 days later</td>
</tr>
<tr>
<td>Leopard, 1971</td>
<td>25 F</td>
<td>Lidocaine 2% + 1:80,000 adrenaline</td>
<td>Diplopia caused by lateral rectus palsy</td>
<td>Immediately after injection</td>
<td>30 min</td>
</tr>
<tr>
<td>Schwartz, 1979</td>
<td>60 M</td>
<td>Lidocaine 2%</td>
<td>Diplopia</td>
<td>N/A</td>
<td>As soon as the anesthetic had worn off</td>
</tr>
<tr>
<td>Petrelli &amp; Steller, 1980</td>
<td>42 F</td>
<td>Mepivacaine 3% without vasoconstriction</td>
<td>Diplopia caused by medial rectus palsy</td>
<td>5 min</td>
<td>90 min</td>
</tr>
<tr>
<td>Kronman, 1984</td>
<td>37 F</td>
<td>Carbocaine</td>
<td>Diplopia</td>
<td>3–4 min</td>
<td>50 min</td>
</tr>
<tr>
<td>Goldenberg, 1990</td>
<td>31 F</td>
<td>Lidocaine 2% + 1:100,000 adrenaline</td>
<td>Dizziness, diplopia caused by lateral rectus palsy, numbness and partial paresis of the eyebrow and upper and lower lids</td>
<td>40 min after the completion of the dental treatment</td>
<td></td>
</tr>
<tr>
<td>McNicholas &amp; Torabinejad, 1992</td>
<td>38 F</td>
<td>Lidocaine 2% + 1:100,000 adrenaline</td>
<td>Lateral rectus palsy and dilated pupil</td>
<td>At completion of dental treatment</td>
<td>80 min</td>
</tr>
<tr>
<td>Marinho, 1995</td>
<td>25 M</td>
<td>Lidocaine 2% + 1:80,000 adrenaline</td>
<td>Diplopia caused by lateral rectus palsy</td>
<td>Few min after injection</td>
<td>3 h</td>
</tr>
<tr>
<td>Penarrocha-Diago, 2000</td>
<td>65 F</td>
<td>Articaine 2% + 1:100,000 adrenaline</td>
<td>Ptosis, miosis</td>
<td>N/A</td>
<td>50 min</td>
</tr>
<tr>
<td>**</td>
<td>29 F</td>
<td>Same</td>
<td>Ptosis, miosis</td>
<td>N/A</td>
<td>20 min</td>
</tr>
<tr>
<td>**</td>
<td>53 M</td>
<td>Same</td>
<td>Ptosis, miosis</td>
<td>N/A</td>
<td>40 min</td>
</tr>
<tr>
<td>**</td>
<td>49 F</td>
<td>Same</td>
<td>Lateral rectus palsy, mydriasis, ptosis</td>
<td>N/A</td>
<td>45 min</td>
</tr>
<tr>
<td>**</td>
<td>60 F</td>
<td>Same</td>
<td>Lateral rectus palsy, mydriasis, ptosis</td>
<td>N/A</td>
<td>30 min</td>
</tr>
<tr>
<td>**</td>
<td>25 F</td>
<td>Same</td>
<td>Lateral rectus palsy, mydriasis, ptosis</td>
<td>N/A</td>
<td>60 min</td>
</tr>
<tr>
<td>**</td>
<td>24 F</td>
<td>Same</td>
<td>Superior oblique muscle palsy</td>
<td>N/A</td>
<td>30 min</td>
</tr>
<tr>
<td>**</td>
<td>32 F</td>
<td>Same</td>
<td>Lateral rectus palsy</td>
<td>N/A</td>
<td>45 min</td>
</tr>
</tbody>
</table>
Case 3
A 26-year-old woman underwent root canal treatment in tooth 27 (left upper jaw). She reported loss of vision OS immediately after the procedure. Examination 6 days later revealed a visual acuity of 20/20 OD and 20/200 OS, a relative afferent pupillary defect, and markedly impaired color vision OS. Fundus examination was normal in both eyes. Visual fields revealed an inferior altitudinal defect OS. A computed tomography scan of the orbits and brain demonstrated swelling over tooth 27 with no signs of sinus infection; the orbits and optic nerves appeared normal. She was treated with intravenous methylprednisolone 1 g/d for 3 days followed by oral prednisone 1 mg/kg for 11 days that was tapered down over a few days. Ten days later, visual acuity had recovered to 20/20 OS, the relative afferent pupil defect and color vision deficit had disappeared, and the visual field had returned to normal.

DISCUSSION
We have described two patients with ipsilateral optic neuropathy and one patient with an ipsilateral abduction deficit and a dilated pupil occurring immediately after dental procedures involving the upper jaw. In one patient, the optic neuropathy did not recover; in the other, it recovered completely within 10 days. The single patient with an ocular motor disturbance recovered completely within 1 day.

Thirty-nine cases of ophthalmic complications resulting from dental anesthesia have been published in the English literature since 1960, most of them in dental journals. Thirty-six reports have described transient manifestations that disappeared within 5 hours of administration of the anesthetic. Because of the usually benign and transient nature of the manifestations, most patients were never examined by an ophthalmologist. Therefore, the nature of the deficits is not well documented.

Of the 36 reported cases, 23 have occurred after upper jaw anesthesia (posterior superior or a middle superior alveolar block) (Table 1); 13 have occurred after lower jaw anesthesia (mandibular block) (Table 2). The commonest symptom has been diplopia, mostly secondary to lateral rectus palsy. Other manifestations have been visual loss, ptosis, mydriasis, and Horner syndrome. The exact mechanism by which the anesthetic causes the deficits remains unsettled.

In upper jaw anesthesia, the anesthetic is believed to cause neuro-ophtalmic manifestations by any of the following mechanisms:
1. Simple diffusion from the pterygomaxillary fossa to the orbit through defects in the bone or via the vascular, lymphatic, and venous networks that link these spaces (4,5).
2. Inadvertent injection into the orbit through the inferior orbital fissure (6).
<table>
<thead>
<tr>
<th>Reported cases</th>
<th>Patient age &amp; gender</th>
<th>Solution used for dental anesthesia</th>
<th>Clinical signs &amp; symptoms</th>
<th>Onset</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cooper, 1962&lt;sup&gt;27&lt;/sup&gt;</td>
<td>46 F</td>
<td>Carbocaine 2% + 1:20,000 Neo-cobefrin</td>
<td>Transient amaurosis followed by diplopia due to rt lateral rectus palsy</td>
<td>5 min</td>
<td>5 h</td>
</tr>
<tr>
<td>Blaxter &amp; Britten, 1967&lt;sup&gt;7&lt;/sup&gt;</td>
<td>16 F</td>
<td>Procaine + 1:300,000 adrenaline</td>
<td>Amaurosis &amp; diplopia due to medial rectus palsy</td>
<td>Immediately</td>
<td>30 min</td>
</tr>
<tr>
<td></td>
<td>39 M</td>
<td>Same</td>
<td>Partial amaurosis and dilated pupil</td>
<td>30 min</td>
<td>4 h</td>
</tr>
<tr>
<td></td>
<td>30 M</td>
<td>Same</td>
<td>Diplopia due to lateral rectus palsy</td>
<td>5 min</td>
<td>20 min</td>
</tr>
<tr>
<td>Lavine &amp; Stoopack, 1968&lt;sup&gt;28&lt;/sup&gt;</td>
<td>7 M</td>
<td>Butethamine hydrochloride + adrenaline 1:100,000</td>
<td>Ptoia, dilated pupil &amp; tearing</td>
<td>Immediately</td>
<td>30 min</td>
</tr>
<tr>
<td>Rood, 1972&lt;sup&gt;29&lt;/sup&gt;</td>
<td>24 F</td>
<td>Lidocaine 2% + adrenaline 1:80,000</td>
<td>Dizziness, complete ptosis &amp; lateral rectus palsy</td>
<td>Immediately</td>
<td>Ptosis 20 min, diplopia 45 min</td>
</tr>
<tr>
<td>Cooley &amp; Cottingham, 1979&lt;sup&gt;30&lt;/sup&gt;</td>
<td>19 F</td>
<td>N/A</td>
<td>Dizziness, nausea, diplopia</td>
<td>Immediately</td>
<td>Examination the following day – normal</td>
</tr>
<tr>
<td>Campbell, 1979&lt;sup&gt;14&lt;/sup&gt;</td>
<td>34 F</td>
<td>Carbocaine 2% + Neo-cobefrin 1:20,000</td>
<td>Horner’s syndrome, generalized rash over the left neck, face, shoulder and arm; hoarseness</td>
<td>2-3 min</td>
<td>2 h</td>
</tr>
<tr>
<td>Goldenberg, 1983&lt;sup&gt;13&lt;/sup&gt;</td>
<td>58 M</td>
<td>Lidocaine 2% + 1:100,000 adrenaline</td>
<td>Dizziness, diplopia due to lateral rectus palsy &amp; partial amaurosis</td>
<td>2-3 min</td>
<td>20 min</td>
</tr>
<tr>
<td>Dryden, 1993&lt;sup&gt;31&lt;/sup&gt;</td>
<td>33 F</td>
<td>Lidocaine 2% + 1:100,000 adrenaline</td>
<td>Ptosis &amp; diplopia</td>
<td>30 sec</td>
<td>Up to 90 min</td>
</tr>
<tr>
<td>Spierer &amp; Spierer, 1999&lt;sup&gt;32&lt;/sup&gt;</td>
<td>5 F</td>
<td>3% Mepivacaine</td>
<td>Diplopia caused by lateral rectus paresis</td>
<td>5 min</td>
<td>15 min</td>
</tr>
<tr>
<td>Wilkie, 2000&lt;sup&gt;33&lt;/sup&gt;</td>
<td>4 M</td>
<td>Same</td>
<td>Complete ptosis</td>
<td>5 min</td>
<td>20 min</td>
</tr>
<tr>
<td></td>
<td>45 M</td>
<td>Lidocaine 2% + 1:100,000 Adrenaline</td>
<td>Complete amaurosis, ophthalmoplegia, ptosis &amp; mydriasis</td>
<td>Immediately</td>
<td>25–30 min</td>
</tr>
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</table>

N/A, not available; rt, right.
3. Inadvertent intra-arterial injection into the superior alveolar artery with retrograde flow to the internal maxillary artery and then to the middle meningeal artery. A middle meningeal branch occasionally penetrates the superior orbital fissure and anastomoses with the lacrimal branch of the ophthalmic artery (7,8). In support of this theory is the observation that blanching and anesthesia of the skin of the lateral upper and lower eyelids, supplied by the lacrimal nerve and artery, are sometimes described in conjunction with transient ophthalmic manifestations. The risk of penetrating an arterial lumen increases when using a non-aspirating syringe and injecting rapidly under pressure.

4. Inadvertent venous injection into the pterygoid venous plexus (4,9). From there the solution can reach the orbit through the cavernous sinus which receives drainage from the pterygoid venous plexus via emissary veins through the foramen ovale and drainage from the orbit via the inferior and superior ophthalmic veins. The pterygoid venous plexus also communicates with the inferior ophthalmic vein through the inferior orbital fissure (4,9,10).

5. Inadvertent scraping of the wall of an artery. The trauma sets up a sympathetic impulse that travels from the anterior, middle, or posterior superior alveolar arteries back to the internal carotid plexus and from there through the ophthalmic artery to the orbit. Decreased sympathetic activity would then produce vasoconstriction caused by the unopposed parasympathetic tone that in turn would cause ischemic deficits (11).

The mechanism of transient injury after lower jaw anesthesia can hardly be explained by simple diffusion of the anesthetic solution, because the injection site is too far from the orbit. Instead, the proposed mechanism is inadvertent intra-arterial injection (6,12,13). Because the inferior alveolar artery, a branch of the internal maxillary artery, lies adjacent to the alveolar nerve, an accidental intravascular injection is possible. In fact, the chances of penetrating the inferior alveolar artery during mandibular block are much higher than penetrating the posterior or middle superior alveolar arteries during upper teeth anesthesia, not only because of its proximity to the alveolar nerve, but because its lumen is relatively large.

The mechanism of Horner syndrome after inferior alveolar nerve anesthesia remains difficult to explain. It is proposed that inadvertent cervical sympathetic block results from a misdirected injection into the pterygomandibular space. From there the anesthetic would reach the prevertebral space and cause transient sympathetic chemical denervation (14).

Three cases have been reported in which ophthalmic complications were delayed, prolonged, or permanent and thus cannot be easily explained by a direct effect of the anesthetic drug (1–3). Hyams (1) reported a young woman who fainted immediately after the injection. The next day she noticed diplopia. Paresis of third and fourth cranial nerves was diagnosed. Tomazzoli-Gerosa et al. (2) described a young woman who experienced complete hemifacial sensory and motor paralysis immediately after an inferior alveolar nerve block. Several hours later, she lost vision in the ipsilateral eye. Two months later, optic disc pallor was observed, phenomena that resemble our case 2. Another unusual report (3) was that of a 14-year-old girl who “complained of blurred/double vision and occasional light flashes” in her OS 4 hours after the dental treatment was completed. The symptoms persisted the next morning and finally disappeared approximately 24 hours after the injection. No explanation is given.

Permanent loss of vision has been reported after anesthetic injections in other parts of the face, particularly during rhinosurgical procedures (15–17). In these cases, visual loss has been attributed to the vasospastic effect of adrenaline. This supposition is supported by the finding that ophthalmic artery pulse pressure is reduced by 50% after retrobulbar injections of Xylocaine and adrenaline (18).

In our case 1, diffusion of the anesthetic to the orbit or cavernous sinus alone could have explained the ophthalmic manifestations because they disappeared as the anesthetic effect wore off. Our case 2 experienced a permanent loss of vision with a course that resembled anterior ischemic optic neuropathy. We believe that the vasospastic effect of the adrenaline may have triggered this process. We cannot entirely rule out a coincidence, inasmuch as the same condition occurred in the fellow eye 1 year later without an identifiable trigger.

Our case 3 is difficult to explain because the period of optic neuropathy lasted longer than the anesthetic effect. It is possible that the neuropathy was secondary to the effect of lidocaine. Animal studies have demonstrated a possible toxic effect of lidocaine on rat retinal ganglion cells (19).

REFERENCES

Anti-Hu Paraneoplastic Syndrome Presenting as Bilateral Sixth Cranial Nerve Palsies

Tarek Hammam, FRCS, Robert M. McFadzean, MD, and James W. Ironside

Abstract: A 62-year-old woman presented with diplopia caused by bilateral sixth cranial nerve palsies. Two weeks later, she had bulbar weakness and ataxia. Brain magnetic resonance imaging showed non-specific abnormalities and spinal fluid was acellular but contained an elevated protein and oligoclonal bands. A paraneoplastic screen showed anti-Hu antibodies. Her clinical condition improved with immunoglobulin and systemic corticosteroid treatment. Breast cancer was diagnosed 21 months later by mammography but there were no metastases detected. Four and half years after the onset of her diplopia, she died of diffuse metastatic breast cancer. This is the first reported case of anti-Hu paraneoplastic brain stem encephalitis presenting with sixth cranial nerve palsies.


The paraneoplastic syndromes are a group of rare immune-mediated disorders associated with cancer (1). High-titer autoantibodies may be found in the patient’s serum and cerebrospinal fluid that are directed against neurons and the primary tumor. These autoantibodies are considered to be the result of an immunologic response to the primary tumor and may cross-react with cells of the nervous system, causing neuronal damage.

Specific forms of this syndrome are associated with specific anti-neuronal antibodies and tumors. Because the onset of neurologic symptoms often precedes the cancer diagnosis, detection of these antibodies greatly assists investigation for the underlying tumor (1).

Paraneoplastic encephalomyelitis/sensory neuropathy presents with a wide spectrum of neurologic symptoms and signs associated with the anti-Hu antibody ANNA 1 (anti-neuronal nuclear antibody type 1) in 53% of patients. The term “anti-Hu syndrome” is used for patients with the anti-Hu antibody (2). Other antibodies linked with this syndrome include ANNA3, anti-CV2/CRMP5 (collapsing response mediator protein-5), anti-Ta/Ma2, and anti-amphiphysin (3). The clinical spectrum includes diffuse encephalomyelitis, limbic and brain stem encephalitis, cerebellitis, and sensory, motor, and autonomic neuropathies (4). The most frequent underlying tumor is a small cell lung cancer (SCLC). Non-SCLC, neuroblastoma, and cancer of the prostate, stomach, breast, and adrenal gland have been also reported in this syndrome (1).

On immunohistochemical screening for the anti-Hu antibody, the characteristic features are strong staining of the nucleus sparing the nucleolus and faint staining of the cytoplasm in neurons of the central and peripheral nervous system (1). The anti-Hu antibody reacts not only with the patient’s own tumor but also with the small cell lung cancer of other patients.

We report a patient with anti-Hu paraneoplastic brain stem encephalitis who presented with diplopia caused by bilateral sixth nerve palsies.

Case Report

A 62-year-old woman presented with double vision, followed 2 weeks later by hoarseness of her voice, difficulty talking and swallowing, nausea, vomiting, and vertigo related to rapid head turning, tremor of the right arm, and unsteadiness of gait. She reported a weight loss of 28 pounds with a poor diet.

Corrected Snellen visual acuities were 20/30 OD and 20/40 OS. The pupils were equal and reactive to light. Ocular motility examination revealed bilateral weakness of abduction with a primary position 16 prism-diopter esodeviation. Corneal sensation and facial nerve function were intact. The anterior segment examination was unremarkable. Fundus examination showed healthy optic discs and bilateral early retinal pigment epithelial changes in both macular areas. Goldmann visual field assessment was normal OU.

Ear, nose, and throat examination revealed a lateral (cadaveric) position of the vocal cords and bilateral vocal cord palsies. Neurological examination demonstrated impairment of soft palatal movements, brisk upper and lower limb reflexes, facial myokymia, tremor of the right upper
and lower limbs, and truncal ataxia. An intravenous edrophonium (Tensilon) test was negative.

Cranial magnetic resonance imaging showed several foci of increased T2 signal in the centrum semiovale, periventricular region, and one focus in the left cerebellar hemisphere adjacent to the lateral recess of the fourth ventricle (Fig. 1). These findings were considered non-specific. Full blood count, peripheral blood film, random blood glucose, urea and electrolytes, liver function tests, and plasma protein electrophoresis were within normal limits. The erythrocyte sedimentation rate was 6 mm/h. Auto-antibodies including anti-acetylcholine receptor, anti-glycolipid, anti-nuclear screen, complement C3 and C4, extractable nuclear antigens screen for Ro/La/Sm/RNP, anti-nuclear DNA, Crithidia, and rheumatoid factor were all negative. Serum tumor marker studies including alpha-fetoprotein, human chorionic gonadotrophin, carcino-embryonic antigen, and CA 125 were also negative.

Cerebrospinal fluid examination showed no evidence of malignant cells, with a cell count of less than 5 nucleated cells/mm³, an elevated protein level at 1.36 g/L (normal range 0.1–0.5 g/L), and the presence of oligoclonal bands (which were absent from the serum). On immunocytochemical screening for paraneoplastic antibodies in a validated procedure, microscopical examination of sections of rat cerebral cortex exposed to the patient's serum diluted at 1:250 and 1:2500 showed strong evidence of binding to cortical neurons in a pattern consistent with antinuclear (anti-Hu) reaction (Fig. 2) with faint neuronal cytoplasmic staining.

The presumptive diagnosis was brainstem encephalitis as a consequence of the anti-Hu syndrome. Treatment was administered in the form of intravenous human immunoglobulin (0.4 g/kg body weight, 20 g/d for 5 days) and intravenous methylprednisolone 1 g/d for 3 days followed by oral prednisolone 40 mg/d. This treatment appeared to result in a significant improvement in her speech, swallowing, and double vision. She was maintained on prednisolone 40 mg daily for 4 months. Breast palpation, abdominal ultrasonography, and high-resolution computerized tomography scan of the chest on three occasions did not reveal any abnormality. Neurologically she remained stable and was maintained on prednisolone 30 mg/d orally for 30 months. Thereafter the dose was tapered to 5 mg on alternate days until the medication was discontinued 36 months after the start of treatment.

After an interval of 21 months from the onset of her symptoms, she reported a lump in her right breast and mammography revealed evidence of breast cancer. A right simple mastectomy and axillary clearance disclosed an intraductal and infiltrating ductal breast carcinoma (grade III). The invasive tumor had metaplastic spindle cell areas, but there was no definite evidence of vascular or lymphatic channel involvement and the deep excision was free of tumor. Microcalcification was present within the tumor. Three of 12 axillary lymph nodes contained metastatic tumor. She received six cycles at 3-week intervals of cyclophosphamide, methotrexate, and 5-fluorouracil.

Three years after the mastectomy, she was admitted with pain in the left scapular region and a bone scan showed marked irregular uptake of technetium-99 throughout the bony skeleton, an appearance consistent with diffuse metastatic disease. An ultrasound scan of the abdomen revealed numerous hypoechoic areas consistent with metastatic deposits. She was referred to the palliative care team and died 4.5 years after the onset of her initial symptoms.

**FIG. 1.** T2-weighted axial magnetic resonance imaging shows several foci of increased signal in the trigones of the lateral ventricles bilaterally (thin arrows, A) and in the left cerebellar hemisphere adjacent to the lateral recess of the fourth ventricle (thick arrow, B).
DISCUSSION

The Hu antigens are a family of nuclear proteins normally expressed in all neurons of the central and peripheral nervous system (5). The Hu family antigen was first identified in a report of four patients with subacute sensory neuronopathy associated with lung cancer when a serum antibody reacted with the cytoplasm of neurons in the guinea pig cerebral cortex (6). The Hu antigens correspond to a set of proteins of 35 to 40 Kd on Western blot analysis using either neuronal or small cell lung cancer protein extracts. The anti-Hu antibody is a marker not only of sensory neuronopathy but also of encephalomyelitis (5). In the diagnosis of paraneoplastic sensory neuropathies, the sensitivity of anti-Hu antibodies is considered to be 82% and the specificity is 99% (7).

The presence of antibodies against Hu proteins in the serum samples of patients with paraneoplastic syndromes is associated with the destruction of parts of the nervous system and with relative control of growth of the underlying tumor (5). These antibodies identify antigens present normally only in the nervous system (usually in neurons), but for uncertain reasons expressed also in certain tumors. Treatment of the paraneoplastic manifestations may result in a more rapidly growing tumor (5). Substantial evidence suggests that in patients with paraneoplastic antibody-positive serology, the neoplasms grow more indolently and are less likely to metastasize than in patients with the same cancer who are not paraneoplastic antibody-positive or who do not have paraneoplastic manifestations. Recent experimental data in mice support these conclusions (8).

Common findings in paraneoplastic encephalomyelitis are nystagmus and supranuclear vertical gaze palsy, as well as hearing loss, dysarthria, dysphagia, and abnormal respiration. Movement disorders may be prominent (9). Other presenting clinical features include seizures, subacute dementia, and personality changes (limbic encephalitis) (10), a combination that may occur alone or with a sensory neuropathy or cerebellar degeneration.

Painful paresthesias are the dominant symptom of sensory neuropathy and may progress for days to weeks in all four limbs, the trunk, and sometimes the face. All forms of sensation are affected, resulting in a severe sensory ataxia with loss of deep tendon reflexes (11).

A review of 22 reported patients with anti-Ri-associated paraneoplastic syndrome showed that four patients had fourth and sixth nerve palsies, and five patients had other ocular motor abnormalities (12). Our patient presented with double vision caused by isolated bilateral sixth nerve palsies, followed by impaired talking and swallowing, as well as hoarseness caused by bilateral vocal cord palsies because of affection of the recurrent laryngeal nerves. These clinical features, along with associated nausea, vomiting, vertigo, impaired palatal movements, brisk limbs reflexes, facial myokymia, tremor, and truncal ataxia could not be explained by her non-specific magnetic resonance imaging findings.

Magnetic resonance imaging studies of paraneoplastic encephalomyelitis and limbic encephalitis have demonstrated hyperintense temporal T2 signals and contrast-enhanced mesiotemporal signals in T1-weighted images evolving into temporal lobe atrophy over the course of the disease. Multifocal white matter, perithalamic or striatal lesions, as well as cerebellar atrophy, have been also described. However, these imaging changes are non-specific (13,14).

The cerebrospinal fluid may be normal but more commonly shows a mild lymphocytosis and a non-specific increase in protein and IgG and IgG index, sometimes with oligoclonal bands (14).

All therapeutic approaches in the paraneoplastic syndromes must be considered in the light of a possible fluctuating or indolent natural course, spontaneous improvement of neurologic symptoms (15), and even spontaneous tumor regression (16). Eradication of the cancer is the mainstay of treatment, having a favorable influence on the course of paraneoplastic syndromes. The starting point of good clinical management of patients with a paraneoplastic syndrome is early clinical suspicion. Detection of one of the clinically relevant antibody reactivities proves the paraneoplastic etiology. However, even in the absence of
antibodies, a paraneoplastic cause is likely when neurologic symptoms occur within 4 years of cancer diagnosis (whether before or after), the cerebrospinal fluid shows inflammatory changes, and other causes have been excluded, especially if symptoms regress during effective cancer therapy (17).

In patients without known cancer but with a high likelihood of paraneoplastic syndromes, detection of the tumor is essential but may be difficult. Because there is a biologically effective immune response against the underlying cancer, the tumor initially may remain small and localized (18). If specific antibody reactivities are present, they direct the tumor search to specific organs. If the tumor identified does not fit the known specificity of the paraneoplastic pattern, the possibility of atypical expression of relevant antigens (19) or a second malignancy should be considered (20). The use of whole-body positron emission tomography with fluorodeoxyglucose has been advocated for early tumor diagnosis in patients with anti-Hu or clinically suspected paraneoplastic syndromes (21).

REFERENCES


Isolated Vertical Diplopia as the Initial Manifestation of Presumed Pretectal and Anterior Hypothalamic Germinomas

So Young Moon, MD, Ji Soo Kim, MD, Kwang-Dong Choi, MD, Seong-Ho Park, MD, Jeong Min Hwang, MD, and Minsoo Park, MD

Abstract: A 21-year-old man with a 5-month history of diplopia caused by isolated vertical ocular misalignment had normal laboratory studies, including brain magnetic resonance imaging (MRI). Eight months after the onset of diplopia, he reported dry mouth, polydipsia, polyuria, and absent sweating. Examination now disclosed light-near dissociation of the pupillary responses, convergence-retraction nystagmus, and upgaze palsy. MRI revealed enhancing suprasellar and pretectal masses presumed to be germinomas. Two years after brain irradiation and systemic chemotherapy, no lesions are apparent on MRI and hypothalamic dysfunction has partially resolved. In a young patient with isolated vertical diplopia and normal brain imaging, one should consider an early pretectal syndrome and inquire after manifestations of hypothalamic dysfunction.


Intracranial germ cell tumors arise mostly in midline structures, particularly in the suprasellar and pineal regions, and are usually diagnosed between ages 10 and 21 years (1). Suprasellar tumors tend to be located around the hypothalamus, pituitary gland, and optic chiasm, causing autonomic, endocrine, emotional, and visual dysfunction. In most series (2), approximately 90% of pineal region tumors have presented with manifestations of increased intracranial pressure, and approximately 50% have manifestations of a pretectal syndrome.

Although synchronous lesions in the suprasellar and pineal regions have been reported in 13% to 16% of germ cell tumors (3), a detailed description of the sequential development of anterior hypothalamic and pretectal syndromes in a patient with germ cell tumors is not available. We report a patient who presented with a 5-month history of diplopia and an examination that disclosed isolated vertical ocular misalignment. All diagnostic studies, including brain magnetic resonance imaging (MRI), were negative. Within 1 month, he manifested hypothalamic dysfunction and a full pretectal syndrome. MRI now showed pineal and hypothalamic region masses.

CASE REPORT

A 21-year-old soldier was referred for evaluation of vertical diplopia that had been present for 7 months. The diplopia developed gradually and remained unchanged over a few months before the visit. He denied head trauma and other past medical history was unremarkable.

Neuro-ophthalmological examination showed normal visual function, pupils, and eyelids. There was no head tilt. He showed a right hypertropia that increased in left upward gaze and changed into a left hypertropia in left downward gaze. The right hypertropia did not change on tilting the head to either side. He also had incyclotorsion of the OD. Measurement of the subjective visual vertical revealed leftward tilt with both monocular (right: −5.3°, normal range: −3.4° to 2.8°; left: −6.3°, normal range: −3.3° to 2.7°) and binocular (−5.4°, normal range: −3.0° to 2.2°) viewing (4). The titer of acetylcholine receptor antibody was mildly increased at 1.45 nmol/L (normal range 0–0.2 nmol/L). However, repetitive nerve stimulation and intramuscular neostigmine tests were normal. Thyroid function and antibody tests were also normal. Review of the MRI, performed 2 months before the visit (and 5 months after diplopia onset) showed no abnormalities (Fig. 1A–C).

One month later, he reported dry mouth, polydipsia, and polyuria (8 L/day). Also, he said that he did not sweat even after strenuous exercise or a hot bath, with body temperatures elevating up to 40°. However, he showed normal piloerection in the cold. Vital signs were normal without orthostatic hypotension. His ocular misalignment pattern
was unchanged. Now both pupils were dilated at 8 mm in dim illumination with no constriction to direct light but a brisk constriction to a near target. The water-deprivation test documented central diabetes insipidus, which was controlled with oral vasopressin. The sympathetic skin response, Schirmer test, cold pressor test, and cardiovascular autonomic function tests were normal.

One month later, convergence–retraction nystagmus and upgaze palsy developed. Repeat brain MRI revealed enhancing lesions in the suprasellar and prefrontal areas consistent with germ cell tumors (Fig. 1D–F). As part of the evaluation for these brain masses, chest computed tomography was normal. Imaging of the spine was not performed. Complete blood counts were normal. Serum adrenocorticotropic and growth hormones, alpha-fetoprotein, and human chorionic gonadotropin were normal. Pituitary hormones were decreased, including serum testosterone 0.28 ng/mL (normal: 1.6–8.8), thyrotropin 0.05 μIU/mL (normal: 0.4–4.1), and cortisol 1.8 μg/dL (normal: 5–25). Prolactin was elevated at 32.4 ng/mL (normal 1.6–14.9). Lumbar puncture showed a normal opening pressure with 2 lymphocytes/mm³ and 10 red blood cells/mm³. Cerebrospinal fluid glucose, alpha-fetoprotein, and human chorionic gonadotropin were normal. However, protein was mildly elevated at 61.2 mg/dL. Cytology showed a few lymphocytes and monocytes without malignant cells. Biopsy of the lesions was not performed because of the small size and risky location of the lesions and the strong presumption that these were germinomas.

He received chemotherapy with bleomycin, etoposide, and cisplatin, followed by 4500 cGy irradiation to the whole brain. Six months later, the MRI lesions had disappeared and had not reappeared on repeat MRI 14 months after therapy (Fig. 1G–I). A mild upgaze palsy, light-near dissociation

FIG. 1. MRI performed 5 months (A–C), 8 months (D–F), and 14 months (G–I) after onset of diplopia. Left column: T2-weighted axial; middle column: enhanced T1-weighted axial; right column: enhanced T1-weighted sagittal. A–C. Normal scan. D–F. Enhancing prefrontal and hypothalamic masses (arrows). G–I. Normal scan (after treatment of the tumors).
of the pupillary responses, and convergence–retraction nystagmus persisted. He continued to receive hormone replacement with levothyroxine, desmopressin, and prednisolone for residual pituitary–hypothalamic dysfunction.

**DISCUSSION**

Our patient presented with vertical diplopia and typical findings of anterior hypothalamic and preptectal syndromes eventually developed. Even though pathologic confirmation was not available, a diagnosis of germinomas seems reasonable in view of the typical findings on MRI (3), the rapid resolution of the lesions after radiation and chemotherapy (5), and no recurrence over a 2-year follow-up period.

Our patient showed normal heat production in a cold environment but abnormal heat dissipation in a warm environment. He also had central diabetes insipidus. These manifestations can be explained by understanding the anatomy and physiology of the hypothalamus (Fig. 2). Body temperature is regulated by a hierarchical neuronal network of thermoregulatory pathways extending from the hypothalamus and limbic system to the peripheral sympathetic nerves (6). The preoptic anterior hypothalamus and septal areas are important in integrating central and peripheral information for thermoregulation (7). Temperature-sensitive neurons in the anterior hypothalamus monitor the temperature of the blood passing by them, and activate anterior heat dissipation or posterior heat production mechanisms as necessary to maintain body temperature within physiologic range. Stimulation of the anterior hypothalamus and preoptic area induces sweating and cutaneous vasodilatation, which in turn lower body temperature (8). By contrast, stimulation of the posterior hypothalamus causes cutaneous vasoconstriction and shivering, which increases body temperature. Therefore, bilateral lesions of the anterior hypothalamus give rise to heat dissipation failure in warm environments. In our patient, anhidrosis involved the whole body (9), with a normal sympathetic skin response, which suggested anhidrosis of central rather than peripheral origin. The isolated anhidrosis without other sympathetic abnormalities is consistent with selective involvement of the anterior hypothalamic (9).

Bilateral anterior hypothalamic lesions also cause diabetes insipidus by destroying the supraoptic nuclei (Fig. 2). Bilateral lesions of the posterior hypothalamic may result in failure of body temperature regulation in both warm and cold environments because the lesions would involve not only the areas concerned with production and conservation of heat but also the fibers descending from the more anterior heat dissipation areas. The central diabetes insipidus and heat dissipation deficit with normal heat production, observed in our patient, were consistent with an anterior hypothalamic syndrome. The accompanying hormonal
abnormalities suggest additional involvement of the hypothalamopituitary axis.

Our patient initially presented with vertical diplopia and later had other signs of a pretectal syndrome, including light-near dissociation of the pupillary responses, convergence-retraction nystagmus, and mild upgaze palsy. The pretectum contains various structures involved in vertical and torsional gaze, vergence eye movements, and pupillary responses (10,11). Pineal tumors are the underlying lesions in approximately 9% of pretectal syndromes (10). In view of the right hypertropia, incyclotorsion of the OD, and leftward tilt of the subjective visual vertical, the vertical diplopia seems to have represented incomitant skew deviation associated with a leftward ocular tilt reaction (12). Pretectal lesions may give rise to a contralesional ocular tilt reaction by involving the interstitial nucleus of Cajal (13).

In our patient, the acetylcholine receptor antibody was mildly but confoundingly elevated. The specificity of acetylcholine receptor antibody is known to be more than 99% (14). However, false-positives have been reported in non-myasthenic diseases (14).

A notable feature of our case is that it took as long as 9 months to develop the full features of the pretectal syndrome from the time the patient first noted diplopia. Moreover, 5 months after the diplopia began, the only finding on examination was vertical ocular misalignment and the brain MRI showed no abnormalities. The initial MRI seemed to have failed to detect microinfiltration by the tumor. To the best of our knowledge, there has been no previous report of intracranial germ cell tumors presenting with isolated vertical diplopia without pertinent abnormalities on MRI.

Germinomas are generally quite sensitive to radiation therapy (4000 to 6000 cGy), which offers excellent long-term palliation if not cured. In six patients with visual disturbances from suprasellar germinoma, radiotherapy was effective without recurrence of the symptoms during follow-up periods ranging from 2 to 7 years (15). Recently, to reduce the volume and dose of radiation therapy, and to prolong the survival of patients with non-germinomatous tumors, chemotherapy has been combined with radiotherapy in the management of intracranial germ cell tumors (16).

REFERENCES
Reversible Optic Neuropathy Associated With Low-Dose Methotrexate Therapy

Gerry Clare, BSc MRCOphth, Stephen Colley, FRANZCO, Robin Kennett, BSc MD, FRCP, and John S. Elston, BSc, MD, FRCS, FRCOphth

Abstract: A 66-year-old woman had progressive bilateral optic neuropathy with dense central scotomas and dyschromatopsia. She had been taking oral methotrexate 2.5 mg three times per week for rheumatoid arthritis for the previous 10 months (total intake 322.5 mg) without folic acid supplementation. She had never smoked or abused alcohol and her diet was healthy. Serum folate was reduced at 1.6 ng/mL (normal >4 ng/mL) and vitamin B12 levels were normal. After stopping methotrexate and after administration of oral folic acid, she experienced complete recovery of vision. Serum folate levels returned to normal during folic acid treatment but decreased to below normal once folic treatment was stopped. The persistently low folate level remains unexplained and may reflect a genetic defect in folate metabolism. Methotrexate can cause toxic side effects resulting from folate inhibition but has not been shown definitively to cause a reversible optic neuropathy associated with low serum folate.


INTRODUCTION

Intracellular metabolism of folate, part of the B-vitamin complex, involves several regulatory enzymes for which genetic polymorphisms affecting the efficiency of the metabolic cycle have been described (1,2). Both the anti-inflammatory efficacy of methotrexate and its toxicity are complex and at least partly related to its antifolate properties (3-5). The combination of methotrexate therapy and another insult such as a dietary deficiency or a genetically reduced activity of the folate pathway enzymes leads to a decrease in serum folate levels (5,6). One of the consequences of low folate is an elevation of plasma homocysteine (Hcy), which in animal and cell culture studies leads to inhibition of neuronal mitochondrial function by inducing reactive oxygen species (ROS) and ultimately results in neurodegeneration (7,8). The metabolically active papillomacular bundle could be affected preferentially, producing profound bilateral loss of visual acuity and field defects similar to those seen in hereditary optic neuropathies (9).

We present a patient who had a reversible symmetric optic neuropathy with deep central scotomas and dyschromatopsia attributable to methotrexate treatment and abnormal folate metabolism. Although testing failed to disclose the C677→T polymorphism for 5,10-methylenetetrahydrofolate reductase (MTHFR), the most common variant affecting the folate pathway, tests for less common polymorphisms were not performed.

CASE REPORT

A 66-year-old woman was referred with progressive bilateral visual loss over 5 weeks. She had been taking oral methotrexate 2.5 mg orally three times per week for rheumatoid arthritis for the previous 10 months (total intake 322.5 mg) without folic acid supplementation. She had never smoked or abused alcohol, her diet was healthy, and her medical history was otherwise unremarkable.

At presentation, best-corrected visual acuity was 20/200 OU. No relative afferent pupillary defect was present. Ishihara pseudo-isochromatic plate testing showed absent color vision. The optic discs and macula appeared normal. Goldmann field testing showed extensive central scotomas (Fig. 1). General physical and neurologic examination was normal.

Baseline hematological indices were as follows: hemoglobin 11.7 gm/dL, hematocrit 0.380 L/L, and mean cell volume 107.4 fL. Brain magnetic resonance imaging without contrast showed no abnormality. Electroretinography showed normal scotopic and photopic flash responses with retained oscillatory potentials, but the pattern reversal cortical visual evoked potentials (VEP) showed reduced amplitudes bilaterally (right 4 μV, left 3 μV, with normal being >5 μV) with normal latencies (Fig. 2).

Serum folate was reduced at 1.6 ng/mL (normal >4 ng/mL) with a normal vitamin B12 concentration of
FIG. 1. A. Goldmann visual fields performed shortly after presentation and after 10 months of treatment with methotrexate 7.5 mg/w (total intake 322.5 mg) without folic acid supplementation. The fields demonstrate bilateral central scotomas. B. Goldmann visual fields performed 4 months after methotrexate treatment had been stopped. They are normal.

256 pg/mL. Neither red blood cell folate nor plasma HCY levels were measured at this stage.

Methotrexate treatment was stopped and oral folic acid 5 mg/d was commenced. Over the next 4 months, visual acuities improved progressively to 20/15 OD and 20/20 OS with complete recovery of color vision and visual fields (Fig. 1). All hematological indices, including repeat folate levels, returned to normal.

By 6 months, repeat-pattern reversal cortical VEP amplitudes had recovered to 10 µV OD and 9 µV OS (Fig. 2). At this time, folate therapy was stopped. Plasma HCY and serum folate were measured after a 6-month interval free of therapy and found to be abnormal. HCY was 26.3 µmol/L (normal 5.0–15.0 µmol/L) and folate was reduced at 3.70 ng/mL. Testing failed to disclose the C677→T polymorphism for MTHFR, the most common variant affecting the folate pathway. Tests for less common polymorphisms were not performed.

DISCUSSION

The timing of this patient’s visual recovery implicates abnormal folate metabolism as the cause of the optic neuropathy. Untreated dietary B-complex vitamin deficiencies associated with chronic alcoholism or malnutrition typically cause bilateral discrete central or cecocentral scotomas and less commonly precipitate profound visual field defects like those seen here (8). In this case, there was no history of smoking or excessive alcohol consumption. The normal VEP latencies after visual recovery and the normal brain magnetic resonance imaging suggest that the cause of the symmetric reversible optic neuropathy was not demyelination.

This patient’s severe field defects are similar to those seen early in the course of inherited optic neuropathies associated with mitochondrial deficiencies, such as the maternally inherited Leber hereditary optic neuropathy. The derangement in folate metabolism may cause a severe optic neuropathy through an unknown mechanism in which the final common pathway is mitochondrial dysfunction. The optic neuropathy appears to be completely reversible.

Folate deprivation is implicated in a diverse range of disorders including fetal abnormalities and neurodegenerative diseases (1,2). Side effects of methotrexate may be related to its antifolate properties and toxicity involves a wide variety of tissues (3,4). Methotrexate inhibits intracellular dihydrofolate reductase and MTHFR. Dihydrofolate reductase is required to produce tetrahydrofolate (THF), an important substrate in purine and pyrimidine biosynthesis. MTHFR partly regulates production of 5-methyl THF, a cofactor required along with vitamin B12 to remethylate HCY to methionine, which acts as a methyl donor for DNA. Serum folate enters the cell via specialized
FIG. 2. A. Pattern reversal visual evoked potentials (VEP) recorded from a midline occipital electrode at clinical presentation. They demonstrate reduced amplitudes and normal latencies. B. VEP recorded 6 months after methotrexate treatment had been stopped. They are normal. (Amplitude bar 8 μV; two runs superimposed from OU.)

receptors to replenish 5-methyl THF. If folate levels decline, substrates such as Hcy increase and DNA methylation and repair is compromised.

Low levels of serum folate seen in patients on low-dose methotrexate treatment probably result from decreased intestinal absorption of folate (10) and consequent raised levels of Hcy (11). Interruption of remethylation of Hcy is thought to be the mechanism by which vitamin B12 deficiency leads to a neuropathy in which an accumulation of 5-methyl THF is seen (1). Hcy may be neurotoxic by induction of ROS within the cytosol and mitochondria, resulting in disruption of the respiratory chain (8). Electron microscopy studies in rat brains suggest that elevated Hcy levels resulting from decreased folate result in mitochondrial degeneration (7). Our patient’s elevated plasma Hcy and low folate levels, noted after methotrexate and folate therapy were stopped, may indicate either an intrinsically defective folate cycle or inadequate intake of dietary folate. However, elevated Hcy is not commonly associated with non-ischemic optic neuropathy, suggesting that other mechanisms are involved.

A genetic polymorphism C677→T resulting in reduced enzymatic activity has been described for MTHFR and is associated with greater toxicity of methotrexate. Functional polymorphisms have been described for other folate enzymes (2,5). Prevalence of homozygous (TT) genotypes with the C677→T MTHFR polymorphism is estimated to be approximately 12% (6). Our patient does not carry this variant, and tests for the other polymorphisms, which are uncommonly performed, were not performed. Therefore, we may never know whether her folate processing is genetically normal.

In most patients, dietary folate is enough to prevent methotrexate-related folate deficiency manifestations (6). Patients who have side effects at low methotrexate doses despite an absence of related risk factors may have abnormal folate metabolism (5,6).

The dyschromatopsia and symmetrical central scotomas seen in this case may represent an acquired mitochondrial dysfunction of the small metabolically active fibers of the papillomacular bundle. The pre-laminar unmyelinated portion of these fibers is particularly rich in mitochondria (9). The profundity of the visual field defects described here suggest a severe defect in the metabolic pathways involved that would not normally be seen in patients treated with low doses of methotrexate. However, given that the TT genotype is common, as are methotrexate therapy and dietary folate deficiency, it is difficult to know why this clinical picture is not seen more frequently. The widespread supplementation of methotrexate treatment with oral folic acid may mask this finding in the general population.

An isolated low level of serum folate has been implicated in reversible nutritional–toxic optic neuropathy in studies of patients who regularly consumed tobacco and alcohol (12,13) and in an isolated case report of a woman with a poor diet and moderate tobacco use (14). Low-dose methotrexate therapy has also been reported as a cause of optic neuropathy in a woman in whom visual field defects corresponded to dose changes (15) but whose serum folate was not recorded, and in a woman in whom serum folate was found to be normal (16). In both of these patients, transient optic disc swelling was noted, and visual field defects lessened but did not disappear when the drug was stopped.

In our patient, a direct neurotoxic effect of methotrexate cannot be excluded. The dramatic resolution of the optic neuropathy with normalization of the VEP and visual fields on administration of folate therapy suggests that methotrexate precipitated the visual loss. A toxic optic neuropathy should be suspected in any patient in whom painless visual loss develops while using methotrexate therapy, particularly if folate supplementation is not being provided. In such a case, discontinuation of methotrexate treatment may be necessary to prevent permanent visual loss.
should be considered and folate supplements commenced. Electrophysiological testing and visual field testing, coupled with measurement of serum folate and plasma HCY levels, are helpful in establishing the diagnosis and monitoring visual recovery.

REFERENCES

Sustained Visual Recovery After Treatment With Intrathecal Methotrexate in a Case of Optic Neuropathy Caused by Chronic Lymphocytic Leukemia

Lizette Mowatt, FRCS, FRCOphth, Tim Matthews, FRCOphth, and Ioanne Anderson, MBBS, FRANZCO

Abstract: A 68-year-old woman with chronic lymphocytic leukemia (CLL) had acute optic neuropathy associated with cerebrospinal fluid evidence of meningeal spread of CLL. There was no evidence of a hematologic relapse. After undergoing four weekly doses of intrathecal methotrexate, vision improved dramatically and spinal fluid became normal. Four years later, she has near normal vision in the affected eye and remains in hematologic remission. This is the first reported case of successful treatment of optic neuropathy in CLL with intrathecal methotrexate alone.


Central nervous system or meningeal involvement in chronic lymphocytic leukemia (CLL) is uncommon (1–4). Its neurologic manifestations usually consist of neurocognitive dysfunction, cerebellar signs, and cranial nerve palsies (1,5,6). Optic neuropathy in CLL is rare and has been treated successfully with irradiation (2).

This is the first reported case of optic neuropathy in CLL to be successfully treated with intrathecal methotrexate alone.

CASE REPORT

A 68-year-old woman presented with a 10-week history of right periocular pain and reduced vision OD. She had stage A chronic lymphocytic leukemia diagnosed 10 years earlier that had progressed to stage C within 2 years. However, it had been in remission for 7 years.

At her first assessment by our Neuro-Ophthalmology Unit, visual acuity was counting fingers OD and 20/30 OS. The patient had a marked color deficit and a relative afferent pupil defect OD. The OS was normal. Goldmann visual field testing revealed a centrocecal scotoma OD (Fig. 1). Ophthalmoscopic examination and ultrasonography revealed normal optic discs.

Laboratory studies included hemoglobin 11 g/dL, white blood cell count 75.8 × 10^9/L, and platelets 89 × 10^9/L. Cerebrospinal fluid (CSF) analysis revealed small lymphocytes and no evidence of organisms. Immunophenotyping of CSF revealed a predominance of lymphocytes, two-thirds of which belonged to a neoplastic clone of B cells that was positive for CD20, CD5, and lambda, a phenotype consistent with B-cell CLL.

After 3 days of treatment with intravenous methylprednisolone 1 g/d, there was no improvement in vision, so the patient was begun on chlorambucil 5 mg three times daily orally for 6 days and four weekly doses of methotrexate 12.5 mg intrathecally. At completion of treatment, visual acuity had improved to 20/80 OD. She had a persistent relative afferent pupil defect and temporal optic disc pallor OD. Repeat CSF analysis revealed no leukemic cells. Complete blood count showed hemoglobin 11.3 g/L, white blood cell count 6.7 × 10^9/L, and platelets 99 × 10^9/L.

Six months after treatment, visual acuity had improved to 20/30 OD. At 18 months, visual acuity remained 20/30 OD with a residual central scotoma OD (Fig. 2). Four years later, there has been no change in her ophthalmic status and hematological and CSF parameters remain normal.

DISCUSSION

Invasion of the brain, spinal cord, leptomeninges, and dura by B-cell CLL is found in 33% of autopsies of CLL patients but clinical cases are rare (3). Central nervous system and meningeal involvement is generally thought to
be a manifestation of advanced CLL, but it may occur early in the disease and even as a presenting manifestation (2–5). From 16 autopsies of CLL patients with CNS involvement, Cramer et al (1) demonstrated that it may occur across all stages of the CLL. In one series of three cases, optic neuropathy was the first clinical manifestation of previously asymptomatic CLL and the precursor of worsening of the CLL (2).

Factors associated with central nervous system involvement include transformation to a more aggressive variant of CLL (Richter syndrome) (1), thrombocytopenia, and a T-cell variant, which is relatively aggressive (7). Our patient was noted to be consistently thrombocytopenic, although she was not symptomatic from this condition.

Optic nerve involvement is more commonly a feature of acute leukemia than of CLL. It is characteristically
associated with hematological relapses (8), unlike our case. The optic neuropathy may occur with or without optic disc edema. Reduction in vision is postulated to result from distension of the optic nerve septae by leukemic cells, causing axonal compression and impairment of axoplasmic flow (9,10).

CSF analysis and immunophenotyping is necessary to confirm the diagnosis. It is critical in differentiating CLL infiltration from opportunistic infections caused by Herpes viruses, Candida, or Cryptococcus, which may cause a polyclonal B-cell response, and from radiation optic neuropathy. CSF phenotyping is also valuable in confirming the resolution of meningeal CLL after treatment (2).

Currie et al (2) described three cases of optic neuropathy as an early clinical manifestation of CLL and that responded favorably to optic nerve irradiation. Improvement of visual acuity and visual fields occurred at first with the use of high-dose corticosteroid therapy in two of these cases, but the effect diminished as the medication was tapered. All three patients underwent 24 to 30 Gy irradiation to the orbital area. Some visual improvement was noted within 2 weeks of treatment (2).

However, because of the many complications associated with brain and spinal cord x-irradiation, treatment with intrathecal methotrexate alone has its advantages (11–13). In one series of patients with central nervous system involvement in CLL, intrathecal chemotherapy alone produced longer survival than intrathecal chemotherapy combined with cranial irradiation (1). In that series, there were two long-term survivors who had been treated with cranial irradiation alone and had persistent disease localized to the optic nerve, suggesting that irradiation alone may not be effective for optic nerve infiltration (1).

In view of these facts, we elected to treat our patient with intrathecal methotrexate. She displayed a dramatic and sustained visual recovery without any systemic complications. After 4 years, she remains in hematologic remission. To our knowledge, this is the first reported case of optic neuropathy in CLL to be successfully treated with intrathecal methotrexate without cranial irradiation.

REFERENCES
Recurrent Optic Neuritis as the Presenting Manifestation of Primary Hypereosinophilic Syndrome: A Report of Two Cases

Norah S. Lincoff, MD and David Schlesinger, MD

Abstract: Two patients sustained multiple attacks of optic neuritis with persistent visual loss. An elevated eosinophil count was initially considered an incidental finding. Years later, the diagnosis of primary hypereosinophilic syndrome (HES) was confirmed by skin and bone marrow in one patient and by lung biopsy in the other. Treatment with hydroxyurea in one patient and with continuous low-dose prednisone in the other stopped the optic neuritis attacks, resolved systemic manifestations, and stabilized neurologic manifestations. These cases emphasize that primary HES may be a cause of recurrent optic neuritis, and that delay in diagnosis and treatment of primary HES can lead to visual morbidity.


The primary hypereosinophilic syndrome (primary HES) is a hematologic abnormality with a persistent total eosinophil count of greater than 1.5 X 9/L for more than 6 months, evidence of organ system involvement, and no known cause for the eosinophilia (1). In contrast to primary HES, secondary HES is caused by hypersensitivity reactions, allergic diseases, parasitic infection, collagen vascular diseases, or neoplastic disorders (2).

In primary HES, central nervous system complications are common, caused by an eosinophilic-derived neurotoxin and direct infiltration with eosinophilic cells (2). Cranial and peripheral neuropathies have also been reported (3). The kidneys, lungs, heart, and skin are frequently involved.

Ophthalmologic manifestations are reported in 18% of cases, including reduced vision, diplopia, amaurosis fugax, hemianopic field loss, retinal hemorrhages, retinal and choroidal vascular occlusive disease, Adie pupil, ocular hypertension, and keratitis (Table 1) (4–13). Optic neuritis has not been reported.

We present two cases of recurrent retrobulbar optic neuritis as a part of HES that was unrecognized for many years. Once the diagnosis was made and the patient placed on treatment, no further attacks of optic neuritis occurred over several years’ follow-up.

CASE REPORTS

Case 1
A 58-year-old woman reported 16 episodes of acute visual loss in one eye or the other over the previous 9 years. Each attack had caused persistent reduction in vision despite treatment with variable doses of prednisone. She also had systemic hypertension, episodes of transient diplopia, hypersomnolence, imbalance, and a rash on her right leg. Eosinophils had measured 13% and 16% (normal 0%-6%) of total white blood cells on two occasions, a finding dismissed as incidental.

Neuro-ophthalmic examination in November 1994, after 9 years of recurrent attacks of optic neuritis, revealed best-corrected visual acuities of 20/20–3 OD, 20/30 OS. Pupils were briskly reactive to light without afferent pupillary defect. Humphrey visual field testing revealed double arcuate scotoma (Fig. 1A). Ophthalmoscopy showed bilateral attenuation of the nerve fiber layer and optic disc pallor (Fig. 1B). There was an excoriated macular rash over the right anterior tibial surface of her leg.

Previous brain magnetic resonance imaging (MRI) had been normal, but a recent MRI revealed an area of T2-weighted hyperintensity extending from the left internal capsule to the diencephalon and dorsolateral midbrain with intense enhancement on T1-weighted images (Fig. 2A). Treatment with intravenous methylprednisolone 1 g/d for 4 days, followed by a 3-day course of oral prednisone, caused most of her systemic and visual symptoms to improve over 2 weeks, but the symptoms recurred by the third week. At that time, she also reported confusion and left-sided facial...
TABLE 1. Previously reported ophthalmic manifestations associated with primary hypereosinophilic syndrome

<table>
<thead>
<tr>
<th>Source</th>
<th>% of Patients with ophthalmic manifestations</th>
<th>Ophthalmic manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chusid, 1975&lt;sup&gt;4&lt;/sup&gt;</td>
<td>1/14</td>
<td>Diplopia</td>
</tr>
<tr>
<td>Farcet, 1982&lt;sup&gt;5&lt;/sup&gt;</td>
<td>1/1</td>
<td>Retinal arteritis</td>
</tr>
<tr>
<td>Fauci, 1982&lt;sup&gt;6&lt;/sup&gt;</td>
<td>9/50</td>
<td>Retinal occlusive disease</td>
</tr>
<tr>
<td>Binaghi, 1982&lt;sup&gt;7&lt;/sup&gt;</td>
<td>1/1</td>
<td>Retinal occlusive disease</td>
</tr>
<tr>
<td>Chaine, 1982&lt;sup&gt;8&lt;/sup&gt;</td>
<td>1/12</td>
<td>Episcleritis</td>
</tr>
<tr>
<td>Spry, 1983&lt;sup&gt;9&lt;/sup&gt;</td>
<td>1/15</td>
<td>Retinal vascular disease (arterial occlusive disease, choroidal infarction, microaneurysms, and capillary dropout)</td>
</tr>
<tr>
<td>Moore, 1985&lt;sup&gt;10&lt;/sup&gt;</td>
<td>1/52</td>
<td>&quot;Visual impairment&quot;</td>
</tr>
<tr>
<td>Catalano, 1988&lt;sup&gt;11&lt;/sup&gt;</td>
<td>1/1</td>
<td>Retinal embolus; homonymous hemianopia</td>
</tr>
<tr>
<td>Guidetti, 1991&lt;sup&gt;12&lt;/sup&gt;</td>
<td>1/3</td>
<td>&quot;Optic atrophy&quot; (no history given)</td>
</tr>
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weakness. A repeat MRI showed new areas of hyperintensity and enhancement in the right internal capsule extending into the midbrain and pons (Fig. 2B); the previously noted left-sided abnormalities were resolving. After re-treatment with intravenous methylprednisolone, her symptoms resolved again within 1 month and MRI showed substantial resolution of signal abnormalities (Fig. 2C).

FIG. 2. Case 1. Serial magnetic resonance imaging (MRI) scans. A. November 1994. T2-weighted images (top) show high signal involving the left internal capsule and ventral midbrain; these areas enhance on T1-weighted images (bottom). B. December 1994. T2-weighted images (top) show high signal involving the right greater than internal capsule and right ventral midbrain; the right-sided lesions enhance on T1-weighted images (bottom). C. January 1995. T2-weighted images show partial resolution of signal abnormalities noted 7 weeks earlier. D. May 1996. T1-weighted image shows enhancement of the left optic nerve during an attack of acute optic neuritis OS.

A lumbar puncture revealed eight white blood cells with 50% granulocytes and 50% lymphocytes, a protein of 53 (normal 15–45), and no oligoclonal bands.

Normal studies included a standard chemistry profile, sedimentation rate, ANA, dsDNA, ssDNA, ACE, SPEP, Lyme titer, RPR, and thyroid function profile. The eosinophil percent was 10.6% with a total count of 792/mm$^3$ (upper limit of normal = 450/mm$^3$). Treatment with corticosteroids reduced the eosinophils to less than 5% within 1 month. Skin biopsy demonstrated fibrosis and a perivascular inflammatory reaction consisting of numerous eosinophils, lymphocytes, and histiocytes (Fig. 4). Bone marrow biopsy demonstrated moderate eosinophilia in both the aspirate and biopsy (15% eosinophils) with two lymphoid aggregates (Fig. 5). The diagnosis of primary HES was established.

After institution of hydroxyurea (500 mg twice daily), she noted a marked improvement in hypersomnia and in the skin rash. Visual acuity improved to 20/20 OD, 20/25 OS, with slight improvement in visual fields (Fig. 6). She has remained stable on treatment with...
hydroxyurea (500 mg three times daily) for 5 years and has not been treated with prednisone for 3 years.

Case 2

A 46-year-old woman had had three attacks of retrobulbar optic neuritis over 11 years. Vision had improved or stabilized within 1 month of each attack after treatment with prednisone or intravenous methylprednisolone. She had reported transient sensory numbness in her hands and feet lasting several minutes, episodic severe fatigue that resolved with rest, and episodic imbalance lasting for seconds. She had persistent visual loss OD and numbness of the right hand.

Brain MRI had disclosed high T2-weighted signal in the peri-ventricular white matter bilaterally. Lumbar puncture had shown no abnormalities of IgG synthesis, but had shown two oligoclonal bands in the gamma region (none in the serum). She carried the diagnosis of atypical multiple sclerosis for 15 years.

Previous blood counts had shown eosinophilia between 24.4% and 59% and an eosinophil count as high as 1700/mm³, which had been dismissed as incidental. In 1998, she had symptoms of upper airway disease that consisted of cough, reactive airway disease, and pleuritic chest pain. Her O₂ saturation was 92% to 95%. A chest computed tomography demonstrated a pleural effusion, hilar adenopathy, and bilateral infiltrates. Bronchoscopic lung biopsy revealed an eosinophilic infiltrate consistent with pulmonary interstitial eosinophilia. A diagnosis of primary HES was made and she was placed on prednisone 10 mg every other day.

FIG. 4. Case 1. Skin biopsy in May 1996 shows endothelial thickening and infiltrate of eosinophils, lymphocytes, and histiocytes.

Neuro-ophthalmologic examination 2 years later revealed best-corrected visual acuities of 20/40 OD, 20/20 OS, a right afferent pupil defect, and a cecocentral scotoma OD by Humphrey visual field testing (Fig. 7A). Disc pallor was present in both eyes (Fig. 7B). Neurologic examination revealed diminished pinprick sense over the fourth and fifth digits of her right hand and mild hyperreflexia of the right arm. In the succeeding 4 years, she has had no recurrent neurologic or ophthalmologic symptoms.

DISCUSSION

Our two cases of primary HES are unusual in that recurrent optic neuritis, not previously reported in this condition, was a presenting manifestation.

Primary HES is an idiopathic leukoproliferative disorder marked by an eosinophilia of greater than 3% (14,15). Untreated cases are characterized by the presence of more than 1500 eosinophils/mm³ for more than 6 months or an eosinophilia more than 20% of the peripheral total white cell count together with organ damage attributed to the eosinophilia. There is no direct relationship, however, between the eosinophil count and the severity of the clinical complications. The number of degranulated eosinophils may be more important than the total number of eosinophils (16,17). Confirmatory tests of primary HES include skin or bone marrow biopsy, which show increased numbers of mature eosinophils suggesting increased generations of eosinophils. More common in men than women (9:1), primary HES tends to occur between the ages of 20 and 50 (2,19). Although it may manifest acute cardiac or neurologic complications, it tends to be insidious in onset. Pruritic rashes, daytime hypersomnolence, tiredness, cough, shortness of breath, fever, myalgia, and angioedema are common early symptoms. The major cause of mortality is heart disease (3).
Neurologic complications occur in up to 65% of primary HES patients, who may present with encephalopathy, sensory polyneuropathy, cranial neuropathy, or stroke (10). Eosinophils, found in the involved tissues, are thought to cause damage by local degranulation of toxic eosinophilic proteins such as eosinophilic cationic protein and eosinophil major basic protein (18). Some reports have suggested that axonal damage is caused by increased endoneurial pressure from leakage of damaged capillary endothelium, whereas others blame eosinophilic cationic proteins (19). Similar pathologic changes, including infiltration of the myocardium with eosinophils, are seen in the muscles of patients with eosinophilic myositis, whose biopsy samples show necrosis, thrombosis, and fibrosis.

Neurotoxicity caused by eosinophils was first described in 1933 by Gordon and called the Gordon Phenomenon (20). Injected intrathecally into test animals, eosinophil-derived neurotoxin produced loss of Purkinje cells and spongiform vacuolation in the white matter of the cerebellum, brain stem, and spinal cord (21,22).

Fluctuating corticosteroid-responsive white matter MRI lesions are commonly seen in patients with neurologic complications of primary HES. They are attributed to a regionally active inflammatory process with destruction of the blood–brain barrier provoked by eosinophilic-derived neurotoxin (21). Unlike demyelinating plaques or the lesions seen in central nervous system vasculitis, the MRI lesions largely resolve within weeks of initiating corticosteroid treatment, as in our case 1 (Fig. 4).

Treatment with corticosteroids usually induces only temporary remission in HES. In patients unresponsive to corticosteroids, or who are corticosteroid-intolerant, hydroxyurea, a DNA inhibitor, has been used effectively. It works by lowering the peripheral blood eosinophil count (18). Other chemotherapeutic agents that suppress peripheral eosinophilia, including azathioprine, cyclophosphamide, vincristine, cyclosporine, and interferon alpha 2b (23), agents are usually reserved for refractory cases (2).

There is a previous case report of a patient with optic neuritis and primary HES, but the optic neuritis was considered incidental (12). In another report of a series of
primary HES patients, “optic atrophy” was noted in one patient but was not further described (10).

Early recognition of HES, with institution of appropriate treatment, can decrease the visual morbidity from recurrent optic neuritis. Hydroxyurea is a useful corticosteroid-sparing agent in this condition.

REFERENCES
Permanent Visual Deficits Secondary to the HELLP Syndrome

Marjorie A. Murphy, MD and Mitra Ayazifar, MD

Abstract: A 34-year-old woman with eclampsia and the hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome developed encephalopathy, cardiomyopathy, pulmonary edema, liver failure, and disseminated intravascular coagulation (DIC), all of which resolved. She also had retinal hemorrhages in both eyes and a hemorrhagic infarct in the left occipital lobe that resulted in a permanent right homonymous hemianopia and a persistently depressed acuity of 20/100 OS. This case is unusual in demonstrating permanent visual deficits. In nearly all cases of pre-eclampsia or eclampsia, visual deficits are reversible. The superimposition of the HELLP syndrome may create more neurologic damage. Clinicians should be alert to patients at risk for HELLP syndrome and manage them aggressively.

(Hemolysis, elevated liver enzymes, and low platelet count (HELLP) may accompany hypertension and proteinuria (preeclampsia) and seizures (eclampsia) as part of a spectrum of hypertensive disorders of pregnancy (1,2). The HELLP syndrome may be considered a severe variant of preeclampsia/eclampsia (3), or a separate disorder with features that overlap preeclampsia/eclampsia (4–7).

The HELLP syndrome may cause hepatic rupture, disseminated intravascular coagulation (DIC), acute tubular necrosis, pulmonary edema, adult respiratory distress syndrome, and hemorrhage (8). The incidence of maternal mortality in the HELLP syndrome has been reported at 1% to 4% (5–8), whereas perinatal mortality has been estimated at 10% to 20% (5,9–11).

Although visual disturbances occur in 20% to 25% of patients with severe preeclampsia and eclampsia (12,13), most patients demonstrate complete resolution within several weeks. The few reported cases of ophthalmic manifestations in the HELLP syndrome do not describe major persistent visual loss (8,14–19). We report such a case.

CASE REPORT

A previously healthy 34-year-old white woman had preeclampsia at 33 weeks of gestation. Blood pressure was 158/94 with hemoglobin 11.7 g/dL, hematocrit 33.7%, platelet count 134,000/mL, creatine 0.8, and SGOT 28 U/L. She was treated with betamethasone 12 mg intramuscularly on admission and at 24 hours for preeclampsia and placed on bed rest. Over the next 48 hours, her blood pressure was 134 to 158 systolic, 68 to 80 diastolic.

On the third day after diagnosis, her blood pressure increased to 188/96 and she reported severe epigastric pain, nausea, and vomiting, followed by gross hematuria. Increased facial and extremity edema was noted. She then experienced a tonic-clonic seizure and was treated with magnesium sulfate 10 mg intramuscularly. At that point, she first reported blurred vision in both eyes. A laboratory workup revealed platelets 22,000/mL (150,000–400,000/mL), SGOT 2997 U/L (12–30 U/L), SGPT 1843 U/L (5–32 U/L), and lactate dehydrogenase (LDH) 2717 U/L (85–200 U/L). Based on these clinical and laboratory findings, eclampsia accompanied by the HELLP syndrome was diagnosed.

The patient was transfused with platelets, fresh-frozen plasma, and packed red blood cells before induction of labor. A healthy 4-lb 12-oz infant was delivered vaginally. On the first postpartum day, the patient had pulmonary edema, and blood gases were consistent with acidemia and hypoxia. She was treated with intravenous furosemide 20 mg intravenously and labetalol 10 mg intravenously with a peak blood pressure of 170/116. She was placed on a protocol of intravenous mannitol, labetalol, hydralazine, and sublingual nifedipine to maintain the systolic blood pressure at less than 150 mm Hg.

She was drowsy and confused but still reported persistent blurred vision in both eyes and an inability to recognize family members. A brain computed tomography (CT) showed a large left occipital hematoma with mass effect and a midline shift. These findings were confirmed on magnetic resonance imaging (MRI) 2 days later (Fig. 1), which also...
showed interstitial edema in the right parietal and occipital lobes, findings suggestive of the posterior reversible encephalopathy syndrome (PRES).

Based on laboratory findings, the patient had disseminated intravascular coagulation (DIC), with a prothrombin time (PT) 17.5 seconds (11.8–13.8 sec), partial thromboplastin time (PTT) 39.7 seconds (24–35 sec), fibrin degradation products (FDP) 40–80 μg/mL (<10 μg/dL), and fibrinogen 94 mg/dl (194–400 mg/dL). A chest x-ray confirmed florid pulmonary edema, and an echocardiogram revealed a severe cardiomyopathy with an ejection fraction of 26%. Over the next several days, her laboratory findings, including platelet counts and liver enzymes, began to normalize. With aggressive diuresis and cardiopulmonary monitoring, her cardiac ejection fraction improved from 26% to 55% with normalization of blood pressure.

On the fifth postpartum day, visual acuity was counting fingers OD and hand movements OS. Confrontation visual fields revealed a right homonymous hemianopia and a central scotoma OS. The anterior segment examination was unremarkable.

Ophthalmoscopy OD showed a superior disc hemorrhage and diffuse intraretinal hemorrhages (Fig. 2). Ophthalmoscopy OS disclosed optic disc edema, diffuse intraretinal hemorrhages, a preretinal hemorrhage inferonasal to the optic disc, and a large preretinal hemorrhage overlying the macula (Fig. 2). A subsequent Humphrey visual field 30–2 confirmed the right homonymous hemianopia with a central scotoma OS (Fig. 3).

Over the next 3 weeks, the patient's general condition gradually improved, with partial resolution of the left occipital hematoma by CT. A bedside neuropsychologic evaluation 3 weeks postpartum revealed inattention, perseveration, and uncertainty in making simple decisions, impaired visuospatial ability and memory, achromatopsia, and visual object agnosia. She could identify objects tactilely, although inconsistently. Her copying of a complex figure was impaired, with mild distortions and a significant number of missing elements.

Four months postpartum, the patient's visual acuity had improved to 20/25 OD and 10/180 OS. The large preretinal hemorrhage in the OS appeared less dense and was noted to extend into the vitreous. The patient had regained her ability to identify colors and was now able to read simple children's books but not newspapers. She continued to have difficulty with visual recognition of objects. She could not recognize familiar individuals on sight but could recognize them once they spoke (prosopagnosia). A brain MRI (Fig. 4) showed an evolving hematoma with
encephalomalacia in the left occipital lobe and resolution of the vasogenic edema in the right parietal and occipital lobes consistent with PRES.

One year postpartum, the patient’s visual acuity was 20/25 OD and 20/100 OS. Ophthalmoscopy OS showed diffuse pigment mottling in the macula in the area of the previous preretinal hemorrhage. A Humphrey visual field 30–2 showed a persistent right homonymous hemianopia, denser superiorly, and a central scotoma OS. Based on her neurovisual deficits, the patient remained permanently disabled from her previous job and continued to require assistance in caring for her family.

DISCUSSION

Our patient with eclampsia and the HELLP syndrome had a persistent right homonymous hemianopia from a hemorrhagic occipital lobe infarct, subnormal visual acuity OS caused by a retinal hemorrhage, and visual recognition deficits attributed to posterior bihemispheric cerebral ischemia.

Although visual scintillations, visual perceptual impairments, and visual loss are well-recognized manifestations of preeclampsia/eclampsia (20–22), they are usually transient. These ophtalmic manifestations are attributed to PRES, characterized by headaches, altered mental status, seizures, and visual loss associated with predominantly posterior cerebral hemispheric vasogenic edema involving both gray and white matter (22–24). Although PRES is most commonly associated with hypertension, eclampsia, and preeclampsia, it has also been reported after treatment with various drugs, including cyclosporine A and tacrolimus (22).

The main cause of PRES is acute elevation of blood pressure above the upper limit of cerebral blood flow autoregulation (23). Severe hypertension is not mandatory for PRES to develop, and previously normotensive individuals can have signs of encephalopathy at blood pressures as low as 160/100 (22). The pathophysiology of PRES is also thought to be related to endothelial dysfunction, especially in cases without severe hypertension (23,25). The relatively selective involvement of the posterior cerebral areas may reflect a major susceptibility of this region because of a lesser degree of adrenergic innervation supporting circulatory autoregulation (26,27).

The characteristic imaging pattern in PRES is edema involving the posterior portions of both cerebral hemispheres, especially the parieto-occipital regions, in a relatively
symmetric pattern (22). Although the abnormalities primarily affect the subcortical white matter, the cortex and basal ganglia may also be involved (28,29). MRI shows punctate or confluent areas of increased signal on proton-density and T2-weighted images, and fluid-attenuated inversion recovery (FLAIR) sequences improve the ability to detect subtle signal changes (24). In most patients who have follow-up CT or MRI, these findings regress after appropriate therapy, suggesting transient edema rather than true infarction. However, initial differentiation between a reversible and permanent parenchymal lesion is not possible on the basis of conventional MRI or CT scans (22). Clinical signs and symptoms typically resolve before the imaging abnormalities disappear (28,30,31). Servillo et al (32) reported four cases of PRES in critically ill obstetric patients with eclampsia. In the three surviving patients, neurologic and neuroimaging abnormalities completely or almost completely resolved on follow-up MRI within 1 week. The fourth patient had a subarachnoid hemorrhage related to uncontrolled hypertension and died 2 weeks later.

From 4% to 12% of patients with preeclampsia or eclampsia have the HELLP syndrome (8,11,33). Patients may display one or more aspects of the syndrome: microangiopathic hemolytic changes, elevated liver enzymes, and low platelets. Incomplete expression occurs in 50% of HELLP syndrome patients and does not carry the same risks as complete expression (34). The latter group tends to have a more severe disease process as manifested by an increased risk of postpartum hemorrhage and more complicated recovery (8,34). The diagnosis of HELLP syndrome in the 15% of patients without underlying preeclampsia is often delayed, leading to increased morbidity and mortality in this subgroup (5,8).

Although various investigators agree on the general definition of the HELLP syndrome, they disagree on the precise diagnostic criteria, making comparisons difficult between centers with regard to onset, diagnosis, management, and perinatal outcome (4–6). Patients with the HELLP syndrome are typically multiparous white women with a mean age of 25 years (5,8). Symptoms develop during the second or third trimester. HELLP occurs antepartum in 69% to 80% of cases, the remainder occurring between 48 hours to 7 days after delivery (5,8,34). The majority of cases initially worsen (22).

The presenting symptoms of HELLP syndrome include generalized malaise, nausea and vomiting, right upper
quadrant or epigastric pain, headache, visual changes, and shoulder or neck pain (10,34,35). Weight gain and edema are seen in approximately 50%, with hypertension present in two-thirds of patients (7).

The precise pathogenesis of the HELLP syndrome has not yet been determined. However, the prevailing theory (25,36) is that endothelial injury leads to fibrin deposition, causing activated platelets to release vasoconstrictive substances, leading to further platelet aggregation and consumption at sites of endothelial damage. This leads to the microangiopathic hemolytic changes seen with this syndrome.

Patients with HELLP syndrome are at significant risk for pulmonary edema, adult respiratory distress syndrome, placental abruption, DIC, ruptured liver hematomas, and acute renal failure (8). Stroke is the most common cause of death, with thrombocytopenia and cerebral vasospasm considered major risk factors (4,5,8,15). Given the multiple organ complications and the high maternal and perinatal morbidity and mortality associated with the HELLP syndrome, prompt diagnosis and treatment are essential (35).

The reported risk of recurrent HELLP syndrome in future pregnancies is between 3% and 19%, with the risk of recurrent eclampsia or preeclampsia approximately 20% (37,38).

Whether the posterior hemispheric abnormalities in patients who have eclampsia and HELLP are more likely to lead to brain infarction is unclear. Feske et al (39) reported extensive reversible brain lesions in the posterior circulation on MRI in a patient with eclampsia and HELLP syndrome. That patient’s neurologic examination was normal at discharge 4 days after admission, and follow-up MRI 1 week later demonstrated nearly complete resolution of the T2-weighted signal abnormalities in the occipital lobes, thalami, midbrain, pons, and cerebellum.

Driscoll et al (40) reported multifocal cerebral hemorrhages in a case review of four patients with preeclampsia or eclampsia, one of whom also had HELLP. All four patients had scans showing at least two sites of hemorrhage in the posterior cerebral areas; none had solely anterior hemorrhages. Two had bilateral occipital or parieto-occipital hemorrhages and two patients had normal scans initially, with hemorrhages visible on subsequent studies. The one patient who also had HELLP had the most prominent hemorrhage in the posterior cerebral hemispheres, similar to the findings in our patient. Of the three survivors in that study, two had mild residual neuro-ophtalmologic deficits (bilateral ptosis in one and a small, asymomatic left visual field defect in another) at a 4-month follow-up examination. The third survivor had severe cognitive and visuospatial deficits at 3 months follow-up (40). No details regarding the ophthalmologic examination or visual fields were provided.

Our patient’s striking hemorrhagic complications in both eyes and brain likely resulted from the combination of acute severe hypertension and the marked thrombocytopenia, DIC, and hemolysis of the HELLP syndrome. Notably, the HELLP syndrome patient reported by Feske et al (39) had PRES but no brain hemorrhages. The difference in the outcome between their patient and ours might be attributed to our patient’s significantly lower platelet count (21,000/mL versus 81,000/mL) and higher blood pressure (maximum systolic 190/diastolic 116 versus 172/90).

Among the few reported cases of visual complications in patients with the HELLP syndrome (8,14–19), none has had permanent visual deficits. Burke et al (14) described a case associated with bilateral serous retinal detachments, unilateral vitreous hemorrhage, and dural venous sinus thrombosis, but with complete recovery in all respects. In a series of 442 patients, Sibai et al (8) reported transient serous retinal detachment in 0.9%. There are two reported cases of acute cortical blindness in patients with preeclampsia and HELLP syndrome with full visual recovery 3 to 7 days postpartum (15,16). Some investigators report retinal edema with hemorrhages showing spontaneous resolution after delivery (17). Gonzalgo et al (18) described a patient with the HELLP syndrome who had a central retinal vein occlusion 10 days after delivery. The visual symptoms and ophthalmoscop ic findings spontaneously resolved after 2 months. Hashiguchi et al (19) presented the only previously reported case of the HELLP syndrome with an intracerebral hematoma and associated diffuse cerebral edema. Fifteen days after evacuation of the hematoma, no focal neurologic deficits were noted. However, after experiencing a hypertensive crisis and a convulsive seizure, the patient entered an irreversible coma with fixed and dilated pupils.

Corticosteroids (41–44), plasmapheresis (6,45), and expectant management (46) are all therapeutic modalities undergoing investigation for treatment of the HELLP syndrome. To date, prompt delivery is the only intervention known to improve its clinical course (35,47). Given the poor maternal and fetal outcomes associated with the HELLP syndrome and the potentially devastating visual and systemic complications, early identification of women at risk is essential.

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Persistent Visual Loss After Retinochoroidal Infarction in Pregnancy-Induced Hypertension and Disseminated Intravascular Coagulation

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Abstract: A 40-year-old woman had pregnancy-induced hypertension, disseminated intravascular coagulation (DIC), choroidal infarction, and magnetic resonance imaging (MRI) high-signal abnormalities in the occipital regions. With successful treatment of the hypertension and spontaneous resolution of the DIC, the MRI signal abnormalities resolved, but visual acuity remained decreased because of damage to the retina and choroid. This case demonstrates that pregnancy-induced hypertension, particularly if combined with DIC, may produce infarction of the retina and choroid and persistent visual loss even if the effect of this condition on the occipital lobes is limited to reversible vasogenic edema.

A 40-year-old woman had pregnancy-induced hypertension. She was treated successfully with intravenous labetalol 200 mg twice daily for 2 days to control an initial blood pressure of 210/140, followed by the same dose orally for 5 days. A low platelet count (92,000), a raised fibrinogen level (5.5), and an elevated fibrin degradation product D-dimer (1.6 µg/mL, normal <0.4 µg/mL) indicated disseminated intravascular coagulation, which resolved spontaneously without treatment.

Visual acuity was 20/20 OU after delivery but deteriorated 5 days later to finger counting at 3 feet OU. Goldmann visual fields revealed bilateral central scotomas. Ophthalmoscopy showed pallid retinal edema with scattered hemorrhages at both posterior poles (Fig. 1 top). Fluorescein angiography showed extensive choroidal ischemia in the macular region accompanied by late leakage from retinal vessels OU (Fig. 1 bottom).

Magnetic resonance imaging (MRI) T2 and FLAIR sequences performed 2 days after delivery showed subcortical and cortical high-signal predominantly within the occipital regions bilaterally (Fig. 2A). This signal change was initially believed to represent watershed infarction (diffusion-weighted MRI was not performed). However, a repeat MRI 3 months later showed no abnormalities on the same pulse sequences (Fig 2B).

At 12 months after delivery, visual acuity had improved to 20/200 OD and 20/120 OS and ophthalmoscopy showed bilateral optic disc pallor indicative of inner retinal and/or optic nerve infarction and macular pigmentary changes indicative of choroidal infarction (Fig. 3).

The reversal of the MRI abnormalities indicates that the initial signal change did not represent watershed ischemia, but rather vasogenic edema associated with hypertensive encephalopathy (1). Identical MRI signal abnormalities are seen in patients treated with cyclophilins (cyclosporine or tacrolimus). Discontinuation of the agent leads to clinical and imaging recovery (2,3).

The persistent visual loss in our patient is caused by ischemic damage to the retina and choroid. In most cases of retinochoroidal ischemia in the setting of pregnancy-induced hypertension, the visual prognosis is good (4). In this case, the poor outcome may reflect the superimposition of disseminated intravascular coagulation, itself known to be a risk factor for choroidal infarction (5).

Our case demonstrates that pregnancy-induced hypertension, particularly if combined with disseminated intravascular coagulation, may infarct the retina and choroid...
even if the effect of this condition on the posterior brain hemispheres is limited to reversible vasogenic edema.

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Optical Coherence Tomography in a Case of Bilateral Neuroretinitis

Michael W. Stewart, MD, Paul W. Brazis, MD, Kevin M. Barrett, MD, Benjamin H. Eidelman, MD, and Julio C. Mendez, MD

Abstract: A 42-year-old man had fever, chills, and bilateral visual loss. Visual acuity was markedly subnormal OU and ophthalmoscopy disclosed optic disc swelling with retinal thickening extending into the macula OU, findings consistent with neuroretinitis. Fluorescein angiography revealed optic disc leakage and submacular accumulation of dye OU without retinal vascular leakage. Optical coherence tomography (OCT) showed outer plexiform layer retinal edema and subfoveal detachments. There was evidence of active human immune deficiency virus and cytomegalovirus infections. Several weeks after multidrug therapy, sequential OCT scans documented resolution of the outer plexiform edema and submacular detachments in parallel with improved visual acuity. The OCT findings support the theory that submacular detachments in neuroretinitis result from diffusion of fluid from the optic disc to the outer plexiform layer and through the outer limiting membrane to the subretinal space.


FIG. 1. A. Fundus photographs at presentation show optic disc edema OU. In the OS, there is retinal thickening extending to the fovea and foveal discoloration suggestive of a neurosensory detachment. Inset (left) of fluorescein angiogram OD at presentation shows a 1950 µ circular subfoveal neurosensory detachment; frames of the OS did not show this finding as clearly. B. Optical coherence tomography (OCT) OD (left) and OS (right) at presentation shows subfoveal neurosensory detachments with significant outer retinal edema in the papillomacular bundle. The findings are more pronounced OS. (NFL, nerve fiber layer; GCL, ganglion cell layer; IPL, inner plexiform layer; INL, inner nuclear layer; OPL, outer plexiform layer; ONL, outer nuclear layer; PR, photoreceptor layer; SRF, subretinal fluid.)
A 42-year-old man presented with fever, chills, a syncopeal episode, and recent visual loss in both eyes. He acknowledged homosexual encounters and had lost 80 pounds during the past year.

Best-corrected visual acuities were 20/400 OD and finger counting OS. Pupils measured 5 mm in dim illumination and constricted adequately to light OU without afferent pupillary defect. Visual field examination revealed cecocentral scotomas OU. Ophthalmoscopic examination disclosed rare vitreous cells, moderate disc swelling, telangiectatic surface vessels, and small nerve fiber layer hemorrhages OU. Significant retinal thickening extended into the maculae, but the retina otherwise appeared normal (Fig. 1).

Fluorescein angiography showed hyperfluorescent discs OU with late sub-macular accumulation of dye but no retinal vascular leakage (Fig. 1). Optical coherence tomography (OCT) showed significant outer plexiform layer retinal edema extending from the discs to the fovea and subfoveal detachments (Fig. 1).

Pertinent positive laboratory studies included CD4+ of 86/µL (401-1532), Bartonella henselae IgG of 1:128 (<1:128), cytomegalovirus IgG of 309.5 Au/mL (0–14), cytomegalovirus pp65 of 8/400,000 cells, a positive HIV by Western blot assay, and HIV-1 RNA of >100,000 copies/mL (50–100,000). Brain magnetic resonance imaging and cerebrospinal analysis were negative.

With serologic evidence of HIV and cytomegalovirus infections, treatment with lamivudine/zidovudine, efavirenz, valganciclovir, ciprofloxacin, and azithromycin was begun. Hard exudates appeared in both maculae 11 days after presentation (Fig. 2). During the next 5.5 months, serial OCT studies showed gradual resolution of the outer plexiform edema and subfoveal edema OU, leaving only minimal residual findings in the OS (Fig. 3). Segmental temporal disc pallor developed OU. Visual acuities measured 20/30 OD and 20/400 OS.

Neuroretinitis represents an inflammatory optic neuropathy characterized by increased permeability of deep optic nerve blood vessels, leading to macular edema and lipid exudates in a star pattern. The disease usually runs a 6- to 12-week course, typically with good visual recovery (1). Although neuroretinitis has served as an AIDS-defining infection in HIV patients (2), we are unaware of its being a presenting feature.

Peripapillary neurosensory retinal detachments are believed to result from fluid that escapes from deep optic disc vessels and seeps directly into the subretinal space (3). The fluorescein angiographic and OCT findings in our case are consonant with subfoveal detachments. The fluorescein angiogram showed a 1950µ circular area of dye accumulation beneath the right fovea; the OCT electronic calipers measured a 2005µ diameter neurosensory detachment, in excellent agreement with the fluorescein angiogram. The OCT showed extensive fluid within the outer plexiform layer but no evidence of communication between the neurosensory detachment and the optic disc margin. These findings resemble those of Puliafito (4), who noted substantial cystic outer plexiform layer edema, and a neurosensory detachment that did not communicate with the disc in a patient with an optic pit. Similar exudative neurosensory retinal detachments secondary to macular edema can occur in retinal vascular diseases, suggesting that limited subfoveal fluid accumulation may occur more commonly than previously believed (5).

**FIG. 2.** Fundus photographs 3 months after presentation show macular hard exudates with resolution of optic disc edema OU.
FIG. 3. A. OCT 2 weeks after presentation shows marked resolution of outer retinal edema OU. B. OCT 5 weeks after presentation shows further resolution OD; absence of the foveal depression indicates mild thickening. There is residual subretinal and outer plexiform fluid OS. C. OCT 5 months after presentation shows a normal macular structure OD and a small subfoveal detachment OS.

Because the fluorescein angiogram showed no evidence of retinal vascular or retinal pigment epithelial leakage, the exact mechanism of the neurosensory detachments remains uncertain in our case. Subfoveal neurosensory detachment secondary to macular edema can occur because of protein and fluid movement across the outer limiting membrane (6). We postulate that retinal edema in neuroretinitis occurs primarily by fluid movement from the optic disc into the outer plexiform layer, with secondary transit through the outer limiting membrane, resulting in neurosensory subfoveal detachments.

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Sixth Cranial Nerve Palsy Caused by Compression From a Dolichoectatic Vertebral Artery

Ying Zhu, BS, Keith Thulborn, MD, Kimberlee Curnyn, MD, and James Goodwin, MD

Abstract: A 68-year-old man had an unremitting left sixth cranial nerve palsy immediately after completing a long bicycle trip. High-resolution (3 Tesla) magnetic resonance imaging disclosed a dolichoectatic vertebral artery that compressed the left sixth cranial nerve against the belly of the pons at its root exit zone. It was postulated that increased blood flow in the vessel during the unusually prolonged aerobic exercise precipitated the palsy. Compressive palsies of cranial nerves caused by a dolichoectatic basilar artery have often been documented; compressive palsy caused by a dolichoectatic vertebral artery is less well-recognized.

Sixth Cranial Nerve Palsy

stronger prism. He denied any constitutional symptoms or other ophthalmic or neurologic symptoms. Medical history included hypertension, benign prostatic hypertrophy, and Dukes A colon cancer treated with hemicolectomy in 1988. With a presumptive diagnosis of ischemic left sixth cranial nerve palsy, no brain imaging was performed.

On examination in January 2004, 4 months after onset of diplopia, visual acuity, color vision, pupil size and reactivity, and ophthalmoscopy were normal. He had no ptosis, lid twitch or fluttering eye movements, or lid fatigue after sustained upgaze. Ductions were normal OD, but he had only 50% abduction OS. Measured with Maddox rod and fixation at distance, he had 35 prism-diopters of esodeviation in primary gaze, increasing to more than 40 prism-diopters in left gaze and decreasing to 20 prism-diopters in right gaze.

Two days later he underwent brain imaging with a 3-Tesla magnetic resonance imaging and magnetic resonance angiography that demonstrated a dolichoectatic left vertebral artery compressing the left sixth cranial nerve against the pons at the nerve’s root exit zone (Fig. 1). Erythrocyte sedimentation rate, C-reactive protein, glycated hemoglobin, and cardiac echography were normal. Follow-up examination in September 2004, 12 months after the onset of diplopia, still showed OS abduction limited to 50% and a 25 prism-diopter esodeviation in primary gaze at distance.

Later in September 2004, he underwent left medial rectus recession of 5.5 mm without transposition. Examination in December 2004 demonstrated orthophoria in primary gaze. He was free of diplopia in all gaze positions without need for prism.

Dolichoectasia refers an unusually dilated and tortuous artery. Most often, dolichoectasia is associated with brain stem stroke, but it may also cause compressive cranial nerve palsy (3). Dolichoectasia commonly affects the basilar or carotid arterics (1,2). Our case unusually involved the vertebral artery. We believe this to be the first reported case to show in detail the anatomic relationship between the sixth cranial nerve root exit zone in the pons and a compressing dolichoectatic artery. Given that the palsy occurred after a strenuous aerobic exercise, we wonder if increased flow through this dilated vessel provoked the palsy (4).

REFERENCES

Rehabilitation Strategies for Patients With Homonymous Visual Field Defects

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Abstract: Homonymous visual field defects (HVFDs) are among the most common disorders that occur in brain damage, particularly after stroke. They lead to considerable disabilities, particularly with reading and visual exploration. A variety of different approaches, including optical aids and visual training techniques, have been examined for the rehabilitation of these HVFDs. Despite the considerable ingenuity that has been applied and anecdotal evidence that has accumulated, rigorously controlled trials that clearly establish efficacy of any method are lacking.


Homonymous visual field defects (HVFDs) are among the most frequent consequences of brain damage. Thirty percent of all patients with stroke (1) and 70% of those with stroke involving the posterior cerebral artery have hemianopias (2). Subarachnoid hemorrhages, intracerebral hematomas, and trauma add to this figure (3,4). Patients with HVFDs have particular difficulties with reading and visual exploration that have far-reaching repercussions on their domestic and vocational lives (3,4). In addition, HVFDs are associated with a reduced prognosis for successful rehabilitation from stroke (5–8), particularly when combined with visual neglect or visual sensory inattention (9–12). This article updates a previous review of rehabilitation strategies for patients with HVFDs (1). The topic has also been comprehensively reviewed by Kerkhoff (3) and Zihl (4).

Although rehabilitation strategies for aphasia, motor dysfunction, and cognitive dysfunction are widely used in clinical practice, there are no uniformly accepted treatments for HVFDs, and surprisingly little systematic, evidence-based research in this area. As a result, therapeutic nihilism is often the response to rehabilitation of patients with such problems. However, a number of clinical observations should raise optimism regarding the potential for success with a variety of techniques.

PRINCIPLES UNDERLYING VISUAL REHABILITATION

Visual rehabilitation of patients with HVFDs rests on certain physiologic principles and observations.

First, the traditional view that lesions of the geniculostriate pathway in humans result in complete and permanent visual loss in the topographically related area of visual field has been challenged as it has become clear that the “blind” hemifields of hemianopes may retain certain visual functions (13).

Second, some patients eventually experience varying degrees of spontaneous recovery of their visual defect, depending on the underlying pathology and location of the causative lesion (14,15). Studies using 18-fluoro-2-deoxyglucose positron emission tomography have demonstrated a reduction in the size of the metabolic lesion and improvement in striate cortex metabolism in patients with reversible homonymous field defects, but not in patients with persisting field defects (16). HVFDs caused by ischemia show recovery of full visual field in fewer than 10% of cases (5,17). In patients with complete homonymous hemianopias caused by ischemia, field recovery is largely complete within the first 10 days. Recovery of a partial defect is usually maximal within the first 48 hours and complete within 10 to 12 weeks (5,17). In general, vision returns to the affected field in a sequence starting with perception of light, motion, form, color, and finally stereognosis (5,17). Functional brain reorganization may allow recovery of function after the resolution of peri-infarct edema and reperfusion of the ischemic penumbra. However, the strict unilateral retinotopic representation of the primary visual cortex probably limits the degree of reorganization that has been observed in other neural networks that are organized in a more extended and overlapping fashion (18–20).

Third, patients with established HVFDs perform maneuvers designed to compensate for their visual loss. When viewing simple patterns, hemianopic patients concentrate their gaze towards the blind hemifield rather than toward the center of the pattern, demonstrating what is...
Homonymous Visual Field Defects

Optical aids have been promoted but never subjected to clinical trial in the treatment of patients with HVFDs (31–33). These include mirrors attached to spectacle frames (34), partially reflecting mirrors (beam splitters), and dichroic mirrors (which reflect a red image and transmit a green one) (35), reversed telescopes (36), prisms, wide-angle lenses, and closed-circuit television monitors (37).

Optical aids function in one of two ways: (1) to relocate the image to a part of the visual field not within the scotoma; or (2) to expand the visual field. Relocation replaces one scotoma with another, because the relocated image causes another previously visible part of the visual field to become invisible. Field expansion is therefore the preferable option. This has been performed most successfully with prisms.

Standard Prisms

Prisms have been applied to spectacle lenses to treat HVFDs for more than 30 years with varying anecdotal success. Fresnel prisms work by displacing the images of objects toward their apex and are commercially available as plastic press-on lenses that can easily be applied to spectacle lenses with their bases toward the hemianopic side. Binocular sectoral prisms applied to the hemianopic half of each lens appear to be the most commonly used (38,39). They relocate the image when the patient looks sideways through the prism but cause a scotoma in the primary gaze position. Their use in HVFDs in one controlled trial (38) concluded that the prism-treated group performed significantly better on visuospatial tests but did not demonstrate any functional improvement in activities of daily living. Monocularly fitted sectoral prisms serve to expand the field but cause unacceptable central diplopia (40), which may be overcome by trimming the central area (41). Because of these drawbacks, Fresnel prisms used in this way have never really entered clinical practice. However, two recent modifications offer promise: vision multiplexing and prism adaptation.

Vision Multiplexing

Multiplexing refers to the transmission of two or more signals simultaneously over the same communication channel so that all the information can be separated and used at the receiving end. Vision multiplexing is the general engineering approach used by Peli (31,32) to develop a range of visual aids. Under normal circumstances, the visual system allows a wide field of view of almost 180° at very high resolution, which is achieved by using “temporal multiplexing” and variable spatial resolution (33). The peripheral visual fields are continually monitored at low spatial resolution for targets of interest, which are then fixated by the high-resolution fovea via saccadic eye movements. In this way, high-resolution information from several targets of interest is temporally multiplexed and used to generate a high-resolution view over a wide field, even though at any instant only a fraction of the field is seen at such high resolution.

Any visual disorder, such as hemianopia, disrupts the interplay between central and peripheral vision and interrupts multiplexing. A visual multiplexing aid would aim to multiplex the missing component with the remaining one. For hemianopia, the missing peripheral field should be multiplexed with the remaining high-resolution central field in such a way that the visual system can access and interpret both.

An ideal optical aid for patients with HVFDs would therefore: (1) expand the visual field rather than relocate it; (2) function in all positions of gaze; (3) avoid central diplopia; and (4) reconstruct the interplay of central and peripheral vision. Peli (31–33) has developed a visual aid that uses monocular sectoral prisms that are restricted to the peripheral fields (superior, inferior, or both). The prisms are placed across the whole width of the spectacle lens on the side of the hemianopia, above and below the pupil, and provide peripheral field information that is effective in all lateral positions of gaze. The prism expands the field by causing peripheral diplopia, which is a common feature of normal vision and is therefore tolerated far better than central diplopia. The effect is to cause an artificial exotropia in peripheral but not central vision, which is reminiscent of...
the exotropia that some congenital hemianopes develop as a natural compensatory mechanism (42). A visual field expansion of approximately 20° measurable by standard perimetry has been described in the first 30 patients treated with a 40-diopter prism by Peli (32). Patients have reported improved walking and avoidance of obstacles and appear to accurately perceive the location of objects detected using the device. No formal testing has been conducted, but such an engineering approach offers considerable prospects.

**Prism Adaptation**

Binocular prisms, fitted the full width of the spectacle lens, function to relocate the whole field of view (43). A 20-diopter prism, for example, shifts the image by approximately 10° as long as patients do not neutralize the effect by making a compensatory eye movement of 10°. There is evidence that subjects with normal vision can adapt to the effects of the prism (44). Rosetti et al (45) have recently reported using active prism adaptation in patients with neglect rather than hemianopia. It remains to be seen whether this technique will provide an aid to visual rehabilitation in patients with neglect let alone in those with HVFDs.

**VISUAL TRAINING**

**Blindsight**

Despite total destruction of the striate cortex, or even hemispherectomy, 20% of patients with HVFDs remain able to discriminate, without consciously perceiving, attributes of visual targets that are presented tachistoscopically to their blind hemifields in a forced choice context (46,47). There are several theories concerning the mechanism of this “blindsight” (48,49). One theory is that “spared islands” of striate cortical neurons that have survived injury retain their regular projections to extrastriate cortical regions and mediate residual visual function (50). But when no functional striate cortex remains, as after hemispherectomy, this explanation cannot be valid. In that case, blindsight may be mediated by extrageniculostriate pathways projecting to subcortical structures, including the superior colliculus and the pulvinar, and ultimately to theipsilesional extrastriate cortex via tecto-tectal pathways (48,51,52). An alternative explanation invokes cortical plasticity.

Hemianopes have been taught to detect targets in their defective hemifields using blindsight retraining techniques in which they practice discriminating visual stimuli presented as part of forced-choice paradigms (17,53–56). The consensus had been that this training merely induced patients to make larger saccades into their blind fields, rather than using blindsight. However, recent fMRI (functional magnetic resonance imaging) studies have highlighted an affective component to blindsight in mediating the perception of unconscious emotional expression via the amygdala (57,58) demonstrated by the successful forced choice discrimination of positive versus negative facial expressions projected into the blind hemifield. Further functional studies with these patients have demonstrated successful fear-conditioning (59–61) whereby the presentation of a bland visual stimulus to the blind field is not consciously perceived but produces a fear response in the amygdala. This raises a further potential route for rehabilitation: could blindsight serve to condition useful, adaptive responses in patients?

**Compensatory Oculomotor Strategies for Visual Exploration**

Working with the concept that hemianopes naturally make strategic eye movement adaptations to overcome field loss, several groups have attempted to develop training programs aimed at systematically reinforcing these compensatory eye movements, thereby fortifying and enlarging the functional field of visual search. Normal daily activities apparently do not achieve the same effect.

There is limited evidence that patients can successfully adapt to their hemianopias with training in visual search (1,25,27,30,62). Training programs comprise three major steps: (1) practicing large saccades into the blind field in place of the inappropriately small saccades normally made by hemianopes; (2) practicing visual search on projected slides to improve the spatial organization of eye movements; and (3) applying both techniques to real-life scenarios. Various parameters have been used to judge the success of these techniques, including improvements in response time and error rates during visual search, enlargements in the visual field and visual search field (defined as the perimetrically measured area that a patient can actively scan using eye movements without head movements when searching for a suprathreshold stimulus), and improved proficiency in activities of daily living assessed objectively and with questionnaires.

After training 30 patients with HVFDs in daily sessions, Zihl (62) initially reported that the visual search field expanded from 10° to 30° within four to eight sessions. Kerkhoff et al (30) validated these results with 92 hemianopic patients and an additional 30 patients with hemineglect, whose search field increased from 15° to 35°. In a further study, Kerkhoff et al (27) quantified the functional benefit of this training program. After 25 treatment sessions, 22 patients showed a 50% reduction in the time taken to find objects on a table, complementing the subjective improvement elicited in a questionnaire that rated disability. Error rates and response times in visual search had significantly improved. Significant visual field and visual search field expansion were also confirmed. After treatment, 91% of this group returned to part-time work. Zihl (25) proceeded to record the eye movements of eight
hemianopes before and after training in visual search, and highlighted how the improvements in the organization of their scanpaths contributed to the shortening of their response times (25).

More recently, Nelles et al (29) have trained 21 patients in visual search and found that training improved detection and reaction to visual stimuli without expansion of the visual field. Patients reported significant functional improvements in a daily living questionnaire.

Visual Field Recovery

Enormous controversy has surrounded the question of whether any training techniques can significantly reverse visual field loss in hemianopes (1). In a series of experiments in patients with HVFDs, Zihl (63-65) used a technique that involved repeatedly determining light thresholds at the visual field border (64-66). In most cases, the visual field enlargement did not exceed 5° but there were individual cases with remarkable recovery. Kerkhoff et al (27,30) and Pommerenke and Markowitsch (67) observed minor expansions of the field border by 1° to 6.7° in analogous experiments. Balliet et al (68), however, were unable to reproduce Zihl’s results (see Zihl’s response) (69).

Sabel et al (72) have reopened the debate by publishing a series of experiments based on sounder methodologies developed in response to the deficiencies highlighted in previous publications (70-73). Using a domiciliary PC-based stimulus system, they randomized patients with HVFDs to receive an active visual restitution training (VRT) stimulation program or a placebo stimulus program for 1 hour daily, 6 days per week, for 6 months. In the active VRT program, patients were required to respond with a key press to hundreds of repetitive visual stimuli presented in the transition zone between the intact and damaged visual field sector. Responses were monitored by the computer and the stimulus pattern was modulated in accordance with the responses. Stimuli for the placebo program were presented only at fixation. In the study, 95% of the actively treated patients demonstrated a central visual field gain of approximately 5° into the hemianopic field, an enlargement that restores the parafoveal field that is functionally significant for reading. None of the control subjects improved. Of the patients receiving the active VRT program, 72% reported subjective improvement in vision, compared with 17% of the control group. The authors demonstrated that VRT using a white dot stimulus generalized to color and pattern recognition (70), although additional treatment with specific color or shape recognition training resulted in a more pronounced improvement of those functions (69). This technique has now been commercialized (NovaVision AG) and received approval from the United States Food and Drug Administration in 2003.

To explain the mechanism underlying visual field expansion, Sabel et al (71,74) have hypothesized that regular visual stimulation at the damaged visual field border region by VRT could reanimate surviving neurons, providing small islands of residual vision in the cortical region that subserves that field. Considering that survival of a mere 10% to 15% of neurons in a damaged region has been postulated to be sufficient for recovery of basic visual functions (75), repetitive stimulation may lead to reactivation of these neurons, possibly with expanded receptive fields and improved synaptic connectivity (74).

However, a recently published study by Sabel’s group and scientists in Tübingen, Germany (76), in which the visual field was tested independently using a scanning laser ophthalmoscope that controls for visual fixation, failed to find any significant improvement in the visual field defects, although many of the patients noted a subjective impression that they had benefited from the VRT. In an accompanying editorial, Horton (77) suggests that during VRT visual fixation is inadequately controlled, so the reported mean 5° field recovery could be explained by the frequent saccades hemianopic patients make toward their scotoma to maintain surveillance of blind areas in their visual fields (24,26). The visual field improvement therefore may be a function of the method of visual field assessment and fixation control. In an earlier study in which the visual fields were tested before and after VRT using a Tübingen automatic perimeter, no field improvement was noted, although this was not the case when the visual fields were assessed using the same software program as had been used for the VRT (73).

Reading

Patients with hemianopias have reading difficulties that reflect the laterality of the visual field defect. Left hemianopias cause difficulties with the return eye movements required to find the beginning of a new line. Right hemianopias cause more severe reading difficulties, with loss of the anticipatory parafoveal scanning process and a characteristic reading disorder termed “hemianopic dyslexia” (78,79). This disordered reading is reflected in the disruption of reading eye movement scanpaths, which show prolonged fixations, inappropriately small amplitude saccades to the right, and many saccadic regressions. Patients develop individual tricks to overcome these problems, using rulers to keep to the correct line of text or turning a page of text by 90° so that left-to-right reading becomes above-to-below reading (80).

Several groups have postulated that by retraining and improving the disordered eye movements, reading performance will improve. Computer-based systems should have many advantages in delivering and monitoring VRT programs. A computer-based VRT system designed by Zihl (1,81) was used to train a group of 96 patients with HVFDs.
At the end of training, patients were able to read faster and with fewer errors, and eye movement recordings demonstrated fewer fixations, shorter fixation periods, and larger saccadic jumps. Patients with right HVFDs were more disabled and required more training sessions than did patients with left HVFDs (33 sessions compared with 26), and at the end of training they had not improved as much as those with left HVFDs (1). Kerkhoff et al. (82) used an identical protocol to train a group of 56 hemianopic patients for a period of approximately 3 weeks (mean = 13 sessions). This group also demonstrated improved reading, and for both patient groups the improvement was maintained at a follow-up of 6 months to 2 years (1).

CONCLUSIONS

Although the benefits of rehabilitation in patients with HVFDs are often perceived as offering marginal gain, it is likely that this perception may underestimate their real value because the confidence and boost in self-esteem that they give patients is not recognized. The rehabilitation programs currently available or undergoing trial are complex and labor-intensive, and in general they require relatively specific facilities for their implementation. Therefore, the emphasis is shifting to the development of simple, user-friendly techniques that patients can practice in their own homes, causing minimal disruption to their daily lives.

Whether saccadic visual search training provides a successful treatment of patients with HVFDs remains unanswered, largely because many of the various studies have not been adequately controlled, and have not convincingly demonstrated improvements in visual search performance in activities of daily living. In these studies, patients have acted as their own controls (within-subject repeated measure design) and there are no control groups or placebo treatments. Given that patients can improve their performance in visual search with training, it is now necessary to address the specificity of the technique against a placebo condition. A randomized controlled trial with patients who are not trained is needed to assess therapeutic efficacy. However, because of the heterogeneity of underlying lesions, it would be difficult to ensure that control and experimental groups are comparable. A study with a crossover design may be preferable technically but unacceptably long for patients.

In response to clinical need, visual search training techniques are now available. For example, we have developed a domiciliary rehabilitation tool for patients with HVFDs based on a visual search paradigm that is inexpensive and easy to use (63). We have trained 29 hemianopic subjects in their own homes on a dedicated television monitor using a portable computer. Our data show that most patients not only become significantly faster at performing visual search in the laboratory setting but also perform significantly better in validated activities of daily living. Patients rate themselves as less disabled in a visual disorder questionnaire (63). However, there was no evidence for any visual field recovery. The program is now available to patients on video but still needs validation in a placebo-controlled trial.

With respect to computer-based VRT, the domiciliary PC-based design of the system certainly increases the program’s convenience and cost efficiency. Although the magnitude of visual field expansion appears small (5°), such gains in the central field would unquestionably be useful to patients exploring their immediate environment. However, the most recent study (76) casts doubt on its effectiveness.

There have been great advances in the field of optical aids with Pelli’s pioneering multiplexing technique. However, all optical aids require expert fitting in specialist centers and are available only to a minority. Although definitive evidence of their clinical effectiveness is still lacking, computer-based or video-based visual training programs are potentially more readily available and free of side-effects.

REFERENCES

Homonymous Visual Field Defects


Improving Vision in a Patient With Homonymous Hemianopia

A 54-year-old woman has a right occipital stroke that causes a complete left homonymous hemianopia. Six months after the stroke, her ophthalmologic and neurologic examinations are entirely normal except for the persistent hemianopia, which, on Humphrey perimetry, shows no macular sparing. She reports that her reading has slowed down and that because of her visual field defect, she has been forbidden by her doctor from driving a car.

Is there any intervention that would help her?

Bernhard A. Sabel, PhD:

A closer examination is first indicated to determine if the patient has a presumed “complete” hemianopia or whether the visual field examination actually shows some visual sparing, “areas of residual vision” or “relative defects” (1). I would recommend re-evaluating the patient for residual vision with additional repeated suprathreshold high-resolution perimetry to hunt for such areas of residual vision. If some are present, vision restoration therapy (VRT), a computer-based training program, might improve residual vision (2,3). Even small improvements in visual function offered by VRT can be beneficial to the patient.

If VRT proves ineffective or when no further improvements after VRT are noted, saccadic training could be tried. This might improve the patient’s ability to scan visual scenes with the intact hemifield and this, in turn, might improve visual orientation (4) but not reading or driving.

Susanne Trauzettel-Klosinski, MD:

Six months after the stroke, the patient still has a chance of spontaneous recovery of at least parts of the field defect. After 1 year, spontaneous recovery can no longer be expected. After that point, any improvements could be attributed to training. However, except in the research setting, I suggest that training begin within the first few months of onset of the hemianopia.

There is yet no evidence that any intervention will enlarge the visual field defect in a relevant way. Reports of visual field enlargement after training (3,5) have not been confirmed in controlled studies (6,7). Therefore, I would suggest training to improve saccadic exploration toward the blind hemifield, which has been shown to be effective in compensating for the visual field defect (4,8) and in improving the functional visual field essential in everyday life activities. However, the chance of regaining the prerequisites for driving is low.

To overcome the reading disorder, training of predictive saccades during the return sweep can reduce the difficulties in finding the beginning of the next text line. The use of a slightly eccentric fixation locus improves reading by increasing the perceptual span toward the blind hemifield (9,10). Some have recommended that the patient be taught to read vertically by turning the text although there are no scientific studies to support that recommendation.
Are there any studies that compare the outcomes in patients who have undergone saccadic training to patients who have not undergone such training?

Bernhard A. Sabel, PhD:

No studies are available yet in which two independent groups have been compared—one with saccadic training and the other without. Instead, within-subject experimental designs have been used. Thus, the role of the patients’ expectations and the general effect of working on a computer monitor cannot be separated from a specific “saccadic training” effect. Rigorous experimental standards would mandate a double-blind, randomized, placebo-controlled clinical trial before establishing efficacy of “saccadic training.”

Saccadic training can follow different strategies. One strategy is to train patients to make broader searches (“visual search field”) in the blind hemifield. A second approach is to train patients to make small-scale eye movements toward the blind hemifield. A third approach is to train patients to make small-scale eye movements with the goal of improving reading (11). However, such compensation strategies might actually activate attention and restoration in the border zones, making it difficult to decide how improvements should be interpreted.

According to the work of Kerkhoff (12), approximately 95% of hemianopic patients achieve significant improvements with these saccadic treatment techniques. Although this appears to be an overestimate, the visual field size does increase by an average of 6.7° in 30% to 50% of patients; in other words, compensation may induce restoration (13). Other studies, in contrast, have found enlargement of the visual search field without enlargement of the visual field itself (14,15).

Although some clinics in Germany use saccadic compensation strategies to treat patients with visual field defects, there is currently no firm science that supports widespread use of saccadic training. Compensation might actually inhibit restoration because the patient is trained to use the intact visual field sector only. Therefore, the most rational approach would be to first attempt restoration and then try saccadic training if it is needed. Saccadic training should only be applied to patients when restoration therapy is completed or to those who have no residual vision in the “blind” hemifield, a situation that applies to fewer than 10% of all hemianopic patients.

Susanne Trauzettel-Klosinski, MD:

Several studies have shown an improvement of saccadic performance after a systematic saccadic training (4,8,13,15). Kerkhoff et al (4,13) reported an increase in visual search field size (mean 30°), as well as an improvement of identifying objects visually on a table and a subjective improvement in vision as rated by the patients. Zihl (8) found shorter search times, fewer fixations, and lower repetition rates in the scan path after saccadic training. Pambakian et al (15) described shorter reaction times, faster performance of activities of daily living, and subjective improvement after training. These studies have shown significant improvement in visual search tasks when performance was compared before and after training.

However, none of these studies compared the results with an untreated control group. For assessing a specific training effect, a randomized controlled trial with a control group would be necessary. The study of Zihl (8) is also limited by the relatively brief interval from onset of the lesion to testing (6–18 weeks, mean 11 weeks), so that spontaneous recovery cannot be safely excluded (16,17).

Would your approach to this patient differ if high-resolution perimetry disclosed small islands of intact visual field close to fixation in the impaired hemifield?

Bernhard A. Sabel, PhD:

Such incomplete hemianopias are typically found in approximately two-thirds of patients. In such patients, I recommend vision restoration therapy (VRT) (2,3,19), which is known to increase visual field size by shifting the absolute visual field border and improving detection ability in areas of residual vision. Although such border shifts can easily be seen with routine perimetric testing.
(2,3,19), the change cannot be measured with the more difficult task of the scanning laser ophthalmoscope (SLO), such as the one used in the study of Reinhard et al (7).

To appreciate the issue of task difficulty of the SLO, consider the following: standard perimetry uses simple detection tasks of near-threshold or suprathreshold single dots on a dark or gray background and patients have to respond to the stimulus by pressing a button. In contrast, in the SLO task used in the Reinhard study (7), three black dots (a reverse stimulus) were presented on a bright red background, which perceptually flickers because it is created by parallel laser lines that produce lateral interferences (the "McKay effect"). Furthermore, patients had to verbally report what they were seeing and the experimenter interpreted their verbal reports. This is a more difficult task for a damaged visual system, as evidenced by the fact that visual deficits, as defined by the absolute visual field border, are significantly greater when measured with the SLO than when measured with well-established and standardized perimetry (19).

VRT also improves reaction time (19) and is of practical benefit in subjective vision as assessed by patient testimonials (20). Typically two-thirds of patients benefit from VRT (20). If patients focus their attention on specific subsectors of the visual field during VRT, restoration is significantly greater in those regions (18).

If this patient has reading difficulties, there is a 50% chance that reading would improve after VRT. Such an optimistic prognosis is based on the observation that approximately half of the patients report being better able to read again after VRT (20). Also, in the study of Reinhard et al (7), reading improved significantly in one test but not another. I would expect reading to improve with VRT because the average border shift after VRT is approximately 5° of visual angle, a relevant change if it occurs near the fixation point. Even a 2° border shift near the fovea could improve reading.

Some have speculated that eye movements explain the border shift. However, in unpublished research, when eye movements were monitored with an eye-tracker, no change in eye movement patterns or fixation position was observed after VRT despite significant border shifts in the same patients.

The lack of a border shift measured with the SLO (7) cannot be cited as proof that vision restoration does not take place because: (1) the SLO is insensitive to residual vision; (2) in the same patients, a significant border shift in standard perimetric measures occurs; and (3) subjective benefits are reliably reported by the majority of the patients (20), which is also described in the Reinhard et al study (7).

Susanne Trauzettel-Klosinski, MD:

My approach would not differ even if there were small islands of intact visual field close to fixation in the impaired hemifield. Stimulation in this area could provoke saccadic eye movements towards the stimulus, which can be misinterpreted as a visual field recovery, and it would be more effective to apply saccadic training.

Such spared islands of vision would, of course, improve reading if they were along the horizontal meridian.

Are there any optical devices that would be helpful to this patient?

Bernhard A. Sabel, PhD:

There are no optical devices proven to help the vision of hemianopic patients. Occasionally prisms are used that project the images from the deficient part of the visual field onto the intact side. However, patients tend to get confused by double images on the same side of visual space. Such devices cannot be recommended for clinical use.

Susanne Trauzettel-Klosinski, MD:

Most patients are confused by the double images and disturbances in spatial orientation induced by optical devices used in treatment of hemianopia.

Binocular sector prisms result in field relocation or a shift of the position of the field loss (21). They are not effective in hemianopic patients but have been shown beneficial in patients with hemineglect (22).

Monocular mirrors and prisms have been used to shift the image of the blind hemifield into the normal one to expand the field (23). Monocular sector prisms cause diplopia and confusion. Confusion is the intended effect, because it indicates the appearance of an object, which would not be visible without the prism, inducing eye or head movements toward the blind side. However, the diplopia in the center was very unpleasant to the patients (23). Hedges (24) did report a benefit in 20% of his patients.

Monocular sector prisms limited to the peripheral field, placed across the whole width of the lens, have been reported in a small group of patients to expand the field without central diplopia (25,26).
Do you agree that patients with isolated complete homonymous hemianopias should not be permitted to drive? Are there national regulations in Germany about this? If so, who developed them and are they consistent internationally? How much sparing of the hemianopic field would be necessary to allow safe driving?

Bernhard A. Sabel, PhD:

Patients with complete homonymous hemianopias should not be permitted to drive. The national regulations in Germany require 120° horizontally when the damage is binocular and a normal field when the damage is monocular. These standards are not the same internationally; in fact, such regulations vary within each state in the United States. How much sparing is sufficient for driving is unclear. Patients with visual field defects have performed remarkably well in driving simulators, in which they showed little or no deficit compared with age-matched controls in one study (27). This suggests that their ability to perform driving-like tasks may be better than one would expect.

Susanne Trauzettel-Klosinski, MD:

I agree that patients with isolated complete homonymous hemianopia should not be permitted to drive. The regulations about driving with visual field defects in Germany are based on three levels:

1. The binding regulations of the European Community (28) require that group 1 drivers (private cars) have a horizontal field of at least 120°. In persons with only monocular vision, the visual field has to be normal. In Group 2 drivers (public cars, buses, trucks, transport of other persons), the binocular field has to be normal.
2. The German Law for Driving License (29) further specifies that group 1 drivers have a normal central 30° of field.
3. The German Ophthalmological Society (30) has converted these regulations into a more concrete form. For homonymous hemianopia in group 1 drivers, the visual field must extend at least 120° along the horizontal meridian. It must be normal within 20° of fixation in all directions. It must be normal within 30° horizontally and completely normal within 10° above and below fixation. The other hemifield must be completely normal.

Ophthalmologists normally follow these recommendations but are free to deviate in individual cases.

How many degrees of visual field sparing would allow a patient to read without difficulty?

Bernhard A. Sabel, PhD:

To be able to read an ideal scenario would be to have a “reading window” of intact visual field 5° on each side of fixation.

Susanne Trauzettel-Klosinski, MD:

The minimum visual field required for reading is 2° to the left and right of fixation (31–33). This is the area where the text is seen clearly and covers 10 to 12 letters of newspaper print at a distance of 25 cm. For fluent reading, this “visual span” has to be extended in the reading direction by parafoveal information processing (34) up to 5° or 15 letters.

Using conventional and SLO perimetry, we demonstrated that patients with hemianopia need a minimum of 5° to both sides of fixation to read normally. Less than that amount impairs proper reading of a given line of text by right hemianopes and ability to locate the beginning of the next line of text by left hemianopes (33,35,36).

Some patients with macular splitting have a valuable adaptive strategy: they use eccentric fixation, sacrificing a bit of visual acuity to gain a perceptual area of 1° to 2° to one side of the vertical meridian. This shift of the field defect is crucial for regaining reading ability (9).
Rebuttals

Bernhard A. Sabel, PhD:

Although both of us clearly agree that compensation training currently lacks firm evidence of efficacy, we do not share the same opinion concerning the value of vision restoration therapy (VRT). Building an argument on the only two studies in which vision training was only partially effective or not effective in some measures (6,7) is a misrepresentation. Failing to consider all the experiments showing efficacy of vision training will inevitably produce a biased view that does not do justice to the therapeutic potential of VRT.

Dr. Trauzettel-Klosinski fails to acknowledge that although her own VRT-treated patients did not improve in the SLO task, they did improve significantly in near-threshold (TAP) and supra-threshold perimetry (HRP). This is in full agreement with prospective, double-blind, randomized, placebo-controlled clinical trials (3) and was most recently also observed in a study with 300 patients (unpublished). As in previous studies (3,20), our joint study (7) found that approximately two-thirds of the patients clearly reported subjective improvements. In one of two reading tests, performance also improved significantly after VRT.

At the center of the argument over VRT efficacy, however, is the issue of whether an increased visual field size is caused by an artefact of eye movements towards the hemianopic side. There is no empirical evidence for this claim; any claims to the contrary are speculative. Also, it is true that a small number of hemianopes may saccade toward the hemianopic side, but if they do so at all, they do so irrespective of VRT. No one has observed any additional saccades after VRT. In fact, in the Reinhard study (7), most patients showed rather stable fixation ability without any preferential large saccades after VRT; none showed stable eccentric fixation on SLO or TAP. Second, fixation performance in TAP and HRP was unchanged after VRT. Both experiments used standard, clinically verified fixation control procedures. Additionally, in 12 out of the 16 patients tested, the blind spot position remained identical after VRT, disproving eccentric fixation (19). Finally, if eye movements were the cause of visual field expansion, one would expect the entire visual field border to shift—a phenomenon that was not seen.

To put the “eye movement artefact hypothesis” finally to rest, we have now positively and conclusively shown that visual border shifts occur irrespective of eye movements (data presented at the 2005 NANOS annual meeting). Visual fields were measured in a separate sample of 16 patients with simultaneous eye-tracker recordings to measure eye movement positions before and after VRT. This observation clearly provided evidence that visual field enlargements are not caused by eye movements. Restoration of vision is real. If we focus our therapeutic effort only on training patients to move the eyes around and enlarge the search field with “compensation training,” we force them to use only their intact fields. Continuing on this path misses the potential that residual vision in or near the blind regions has for plasticity and repair. Modern approaches to neurologic rehabilitation in other domains are now focusing on the “forced use” of impaired functional systems with great success. An example is constraint-induced therapy in locomotor rehabilitation. In the visual domain, we should do the same thing—offer a therapy that improves residual visual potential and not send patients home with the message that there is nothing we can do to help them.

Susanne Trauzettel-Klosinski, MD:

The problem with VRT is that the stimulation is performed in the “transition zone” between the seeing and the blind hemifields. An apparent increase in visual field size by a shift of the field border could easily be caused by eye movements towards the hemianopic side. SLO studies on patients with hemianopia have shown that they spontaneously perform frequent saccades towards the hemianopic side (7,37,36). This phenomenon is even more marked if the patient expects a stimulus from the blind side. Accordingly, approximately 50% of patients in the SLO study (7) showed less stable fixation after VRT.

The advantage of SLO perimetry is reliable fixation control. In our study, we used only those responses recorded, whereas fixation was central and stable during stimulus presentation. Another advantage of SLO perimetry is the high spatial resolution (0.5°) that we used in examination of the hemianopic fields. Such spatial resolution cannot be achieved with other perimetric methods. Additionally, there is no light scatter into the seeing hemifield if the inverted stimulus mode is used (black stimulus on bright background).

Because the SLO study (7) focused on absolute field defects, only these were examined. We found no change in the absolute field defects before and after VRT. In principle, relative defects could also be measured by SLO. However, even if there had been improvement from absolute to relative defects, as was reported for high-resolution perimetry (HRP), it is questionable if this finding would have been clinically relevant.

Other effects of VRT reported by Dr. Sabel are not specific. Improved reaction times are an expected effect and should be even more pronounced if the same stimulus is used during training (as with VRT) and outcome measurement (HRP). Subjective improvements of vision cannot be judged without a control group.
Because of reliable fixation control, high spatial resolution, and absence of light scatter, the SLO is the most reliable method to examine the central visual field and especially field borders. The studies on VRT have not proven a restoration of the visual field.

This does not mean that restitution mechanisms should be excluded in principle. However, the effects reported by Dr. Sabel and coworkers are likely to be caused by other factors, such as explorative saccades, a raised level of attention, or other nonspecific effects (38,39).

Editor’s Summary

Homonymous hemianopia, especially when it is complete or nearly complete, can be disabling. In most parts of the world, it means no more driving. Reading becomes extremely difficult. In most other aspects of daily living, patients adapt remarkably well if they do not have neglect and otherwise have their wits. They quickly learn that they do not see on one side and they compensate by turning their head and making frequent saccades into the blind hemifield.

But in an attempt to provide them with a broader field of view, optical devices have been affixed to glasses to bring the blind hemifield into view. These efforts have been a dismal failure. They only make the patient visually confused. Perhaps the multiplexing approach described in this issue of the Journal of Neuro-Ophthalmology will be better.

With the apparent success of rehabilitation for neurologic deficits in other systems, it was natural that the same effort be devoted to hemianopia. This debate is centered on two non-optical efforts: saccadic compensation training—teaching hemianopes to make more efficient saccades into the blind hemifield—and VRT—stimulating relative field defect regions at the edge of absolute defects along the vertical meridian to improve the function of these partially preserved visual regions.

Both debaters support saccadic compensation training, but they are skeptical of its benefits until a properly controlled study is performed. Even so, Dr. Trauzettel-Klosinki recommends it as soon as a major hemianopia is identified. Dr. Sabel recommends it only if: (1) high-resolution perimetry fails to disclose areas of relatively preserved vision within the “blind hemifield;” or (2) patients have completed VRT.

It is no surprise that Dr. Sabel, who has expertise in neuropsychologic aspects of vision, and who founded VRT, vigorously supports this restorative approach. He does so on the basis of research that shows improvement in the damaged hemifield after VRT and patient testimonials of improved vision. His approach is based on the idea that a partially damaged central visual pathway should behave like central motor, language, and attentional systems, which apparently improve somewhat with training. But motor, language, and attentional systems have redundancy in the form of supplementary regions. The success of rehabilitation in motor and attention systems may lie in reinforcing these supplementary systems rather than in fortifying the damaged areas. The retinocortical pathway, which is designed to provide exquisite topographical representation of visual space in the brain, has no such redundancy, no back-up systems. Dr. Sabel is counting on the ability to train visual attentional systems. Whether they participate is open to question. Activation studies (fMRI and positron emission tomography) may tell us more about that.

Dr. Trauzettel-Klosinski, a physician with extensive experience in perimetry and in efforts to improve reading in low-vision patients, disputes Dr. Sabel's results. She argues that the SLO study (7), which allows monitoring of eye movements, did not show any enlargement of the blind hemifield after VRT that could not be accounted for by saccades made into that blind field. Moreover, she says, even if there was a tiny enlargement of the field, would it make any real world difference?

And that, of course, is where this whole business must come to rest. Do any of these trainings really make a difference in the two most important activities affected by hemianopia—driving and reading? I doubt that an extra 5° in the blind hemifield will make a hemianopic person safe on the road. Reading is a different matter. As Dr. Trauzettel-Klosinski's research has shown, gaining 5° in the hemifield may make the difference between a stumbling and a smooth reader. If controlled, masked studies of reading before and after saccadic compensation training or VRT show a major difference, I could become a believer.

REFERENCES


The 2005 International Stroke Conference
New Orleans, Louisiana, February 2–4, 2005

The 2005 International Stroke Conference was held on February 2 to 4, 2005 in New Orleans, Louisiana. There were over 500 posters or platform presentations. Abstracts are published in *Stroke* 2005;36:418–524.

**STROKE PREVENTION**

Anticoagulation with warfarin is widely accepted as the standard of care for stroke prevention in patients with atrial fibrillation. However, clinical trial populations represent a carefully selected group with meticulous follow-up, and the application of these findings to real-world populations is unclear. Brian Gage, MD, Washington University School of Medicine, presented a retrospective chart review of a nationwide sample of more than 23,000 Medicare patients admitted to the hospital with atrial fibrillation and examined adherence to treatment and efficacy of stroke prevention by ethnicity. The mean age of the population was 79 years, with a female predominance. Forty-nine percent of whites, 43% blacks, and 40% Hispanics were prescribed anticoagulation with warfarin at the time of hospital discharge. The proportion of patients who had no follow-up of their prothrombin time within 90 days of discharge was found to be 10% for whites, 21% for blacks, and 17% for Hispanics. Warfarin prescribed at hospital discharge was protective against recurrent stroke in whites (hazard ratio [HR]: 0.6; 95% CI: 0.52–0.70), but not in blacks (HR: 1.5; 95% CI: 0.82–2.79) and Hispanics (HR: 0.93; 95% CI: 0.44–1.95). When these results were adjusted for number of days with appropriate monitoring of coagulation profiles, warfarin was effective for all racial groups. This study highlights the importance of investigating the application of clinical trial results to real-world populations, and also provides further evidence for significant racial and ethnic disparities in health care that must be addressed.

Secondary prevention of stroke has centered on management of co-morbid risk factors such as hypertension, diabetes, and smoking. The MOSES study (MOrbidity and mortality after Stroke–Eprosartan vs nitrendipine for Secondary prevention) enrolled patients with hypertension and a history of ischemic or hemorrhagic stroke within the previous 2 years. Patients were randomized to receive treatment with the angiotensin-2 receptor antagonist eprosartan 600 mg/d or the calcium channel blocker nitrendipine 10 mg/d. In 1352 patients followed-up for a mean of 2.5 years, there was no difference in the amount of blood pressure-lowering between the groups. The primary endpoint was combined mortality along with total cardiovascular and cerebrovascular events (including recurrent events). As compared with nitrendipine, there was a 20% relative risk reduction in the primary endpoint among patients treated with eprosartan. There was also a 25% relative risk reduction for total cerebrovascular events in the eprosartan group, although that effect was not statistically significant when first events alone were considered, likely caused by inadequate statistical power. This study suggests that eprosartan is superior to nitrendipine in secondary prevention of stroke and cardiovascular events in patients with a history of ischemic or hemorrhage stroke. Whether this conclusion applies to other angiotensin receptor blockers remains unknown.

**ACUTE ISCHEMIC STROKE**

Because intravenous tissue plasminogen activator (t-PA) was approved for use in acute ischemic stroke in 1995, there have been no additional agents approved by the Food and Drug Administration, but some new agents have been studied in treatment trials.

The Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systemic t-PA (CLOT-BUST) trial demonstrated that continuous 2-MHz transcranial Doppler (TCD) ultrasound enhances the efficacy of intravenous t-PA in patients with middle cerebral artery occlusion as measured by early clinical improvement and artery recanalization. This trial also demonstrated a trend toward improved 3-month clinical outcome (Alexandrova et al, *N Engl J Med* 2004; 351:2170–2178). Based on the results of this trial, further investigations of ultrasound-enhanced thrombolysis are ongoing. Intravenous microbubbles (MB) have been shown to further enhance ultrasound-assisted thrombolysis in experimental models. TCD and MB-enhanced thrombolysis have been hypothesized to enhance cavitation and therefore mechanical stress on the clot surface, perhaps allowing more sites for t-PA binding. Investigators presented the results of a trial of 103 patients with acute middle cerebral artery occlusion.
All patients received intravenous t-PA within 3 hours, and patients were randomized to receive either placebo TCD monitoring (t-PA group), 2 hours of continuous TCD monitoring (t-PA/ultrasound [US] group), or 2 hours of continuous monitoring together with bolus intravenous injections of galactose-based microbubbles (t-PA/US/MB groups). The 2-hour rate of complete recanalization was 54.5% in the t-PA/US/MB group, 40.8% in the t-PA/US group, and 23.9% in the t-PA group. Recanalization also occurred more rapidly in the t-PA/US/MB group. There was a trend toward early clinical improvement in the t-PA/US/MB group relative to the other groups. These results are preliminary, and longer-term safety and efficacy data are required. TCD remains a highly operator-dependent technology; application of these techniques to the general population will remain a challenge.

Several neuroprotective agents for acute ischemic stroke have shown promise in laboratory models, but the search for an effective neuroprotective medication in humans remains unsuccessful. Myron Ginsberg, MD, University of Miami School of Medicine, presented the results of a dose escalation and safety trial of 25% human albumin. A total of 65 patients with acute ischemic stroke were given human albumin within 16 hours of stroke onset in five escalating dose tiers (mean time of administration was 8.0 ± 3.7 hours of stroke onset). A total of six patients died (all with severe stroke), but none of the deaths was likely albumin-related. Three patients had pulmonary edema requiring diuretics and one patient had congestive heart failure leading to prolonged hospitalization. The study was not powered to determine efficacy and there was no placebo control, but there was a trend toward a dose effect on clinical outcome at 3 months. The National Institutes of Health stroke scale score improved from a mean initial 14.1 to 7.8 at 3 months in the lower-dose tier compared with 16.1 to 3.4 in the higher-dose tier. A phase 3 trial is planned in which albumin will be given within 4.5 hours of stroke onset; recruitment for additional study sites is ongoing.

The application of intravenous t-PA to acute ischemic stroke has been limited by the fact that it must be administered within 3 hours time to be effective. This time limit excludes most ischemic stroke patients because they arrive too late. Are there alternative thrombolytic agents or imaging techniques to identify potential candidates for treatment beyond the 3-hour window? This question was the basis for the Dose Escalation study of Desmoteplase in Acute ischemic Stroke (DEDAS) trial, a multicenter, randomized, double-blind, placebo-controlled, dose escalation and safety trial of a novel thrombolytic agent called desmoteplase. Anthony Furlan, MD, Cleveland Clinic Foundation, presented the results of this study. Patients who presented between 3 and 9 hours from the onset of symptoms underwent perfusion-weighted imaging (PWI) and diffusion-weighted imaging (DWI). If the PWI area was 20% greater than the DWI area (“PWI-DWI mismatch”) and the PWI area was at least 2 cm in diameter (two indicators of a large ischemic penumbra), 38 patients were randomized to a low or high single-dose injection of desmoteplase or placebo. No symptomatic intracerebral hemorrhages occurred in any group despite the 9-hour treatment window. The study was not powered to detect efficacy, but a larger randomized placebo-controlled trial is being planned. The lack of hemorrhages supports the notion that advanced imaging may have a potential role in patient selection for thrombolysis beyond the 3-hour time window.

**INTRACEREBRAL HEMORRHAGE**

Intracerebral hemorrhage is a devastating condition with no effective antidote. The volume of the intracerebral hemorrhage is a consistent predictor of mortality. Early growth of intracerebral hemorrhage with expansion of hematoma has been demonstrated to occur in up to 40% of patients. Activated recombinant factor VII (rFVIIa) is currently approved to treat bleeding in hemophilia A with inhibitors to factor VIII or IX and is undergoing investigation as a potential agent to stop early hematoma expansion in intracerebral hemorrhage. A small pilot trial (38 patients) of rFVIIa in non-hemophilia patients with intracerebral hemorrhage did not produce any adverse events (Mayer et al, *Stroke* 2005;36:74-9). A larger study involved 400 patients randomized to receive placebo or a single bolus injection of rFVIIa in three dose tiers (Mayer et al, *N Engl J Med* 2005;352:777-85). All patients had to have had a computed tomography scan within 3 hours of hemorrhage onset and had to receive the study drug within 60 minutes of the scan. The primary outcome was the mean change in hemorrhage volume at 24 hours, with a secondary outcome of 90-day clinical status. Mean hemorrhage volume increased by 29% in the placebo group compared with 11% in the highest dose tier rFVIIa group (p = 0.015). At 90 days, 69% of patients in the placebo group were dependent on others for daily care or were dead (modified Rankin scale of 4–6), as compared with 52% in the pooled treatment group (P < 0.05). There was a trend toward increased risk of venous thrombosis, myocardial infarction, or ischemic stroke in the treatment group (7% versus 2%). However, there was no increased risk of fatal or disabling adverse events. This is first published report of an effective treatment of intracerebral hemorrhage. Additional studies are required to further demonstrate safety and efficacy in a larger group of patients.

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Idiopathic Intracranial Hypertension

Here we make some comments on the state-of-the-art article by Friedman and Jacobson (1) on idiopathic intracranial hypertension. The authors did not mention the echographic examination of the optic nerve as one of the most important diagnostic procedures to diagnose the presence of high intracranial pressure and to monitor the clinical course of this disease (2). With this technique, it is possible to detect an increase of subarachnoidal fluid within the optic nerve sheaths that is caused by the presence of high intracranial pressure (3–4).

The authors noted that “in some patients, papilledema never resolves completely despite resolution of symptoms and stabilization of visual function.” The reason for this was described several years ago by Hayreh (5), who implanted balloons in the brains of monkeys and showed that papilledema takes 1 to 5 days to appear after intracranial pressure elevations. Acutely elevated cerebrospinal fluid pressure for up to 2 hours or sudden lowering of the pressure to normal does not produce immediate resolution of papilledema. This is caused by the slow process of axoplasmic accumulation, the cause of swelling of the axons in the optic nerve head.

Echography is much more sensitive than optic nerve ophthalmoscopic examination, because it can detect a sudden increase or decrease of intracranial pressure by measuring the diameter of the optic nerve sheath. This diameter depends on the amount of perineural subarachnoid fluid, which increases during high pressure and returns to normal when there is a normalization of intracranial pressure. Echography can thus avoid the need for frequent intracranial pressure measurements that are not risk-free.

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REFERENCES

Author's Reply:

As pointed out by Drs. Rosa, Capasso, and Lanza, orbital echography is an extremely useful tool for determining the presence of papilledema, particularly when there is a question of pseudopapilledema from optic disc drusen or tilted optic nerves. The 30-degree test, a non-invasive and painless office technique, provides documentation of a distended subarachnoid optic nerve sheath in true papilledema that spares needless investigations in patients with other conditions that simulate it. I regret the inadvertent omission of this diagnostic modality in our article.

The lack of resolution of papilledema in the short-term, as described by Hayreh (1), is well-recognized. There are some patients with idiopathic intracranial hypertension who have persistent nerve fiber elevation indefinitely after their idiopathic intracranial hypertension seems to have otherwise resolved. Because the swelling does not progress, an ongoing disorder of axoplasmic flow seems unlikely. Perhaps there are gliotic changes in the nerve fiber layer that prevent the restoration of normal architecture at the anterior surface of the optic nerve. Regardless of the mechanism, from a clinical perspective, life-long ongoing intracranial pressure-lowering agents may not be necessary in these patients.

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REFERENCE

Transient Monocular Visual Loss in Two Patients With Impending Central Retinal Vein Occlusion

Transient monocular visual loss (TMVL) has been reported as a symptom of central retinal vein occlusion (CRVO) with its typical ophthalmoscopic findings (1,2).
FIG. 1. Case 1. A. Moderately dilated retinal veins OD are the only abnormality at the initial examination for transient monocular visual loss (TMVL) OD. B. Two weeks later, retinal veins are more dilated and patchy retinal whitening is evident in the papillomacular bundle OD, signs of a central retinal vein occlusion.

We previously reported a patient with TMVL associated with dilated retinal veins as the only ophthalmoscopic finding (3), and now we report two additional patients. In these two patients, conventional signs of retinal vein occlusion appeared within 2 weeks of the original examination.

Case 1 was a 43-year-old woman who experienced five episodes of painless TMVL in her OD. Each episode lasted from 10 to 40 minutes and resolved spontaneously. She described the episodes as “sudden blurry, dim vision with bright dots” that occurred over a 1-week period without precipitating factors.

Initial evaluation, 2 days after onset of TMVL, showed normal visual function and isolated moderate retinal venous engorgement OD (Fig. 1A). Fluorescein angiography showed dilation of the retinal veins OD with delayed venous filling; arterial filling was normal. Carotid ultrasound was normal bilaterally. Aspirin 325 mg/d was prescribed.

One week later, she reported decreased vision in her OD. Visual acuity was 20/20 OD with mild red desaturation and a small right paracentral scotoma OD on Humphrey visual fields. Ophthalmoscopy now showed mild disc edema with venous dilation, peripapillary retinal edema, and multiple small retinal hemorrhages OD consistent with a CRVO (Fig. 1B). Fluorescein angiography continued to show delayed venous filling OD. An extensive coagulation workup was initially negative (4). Magnetic resonance imaging of the brain and orbits was normal. She was maintained on aspirin. Three months later, visual function improved and the scotoma had resolved. Repeat coagulation workup led to the diagnosis of primary antiphospholipid syndrome. Aspirin was replaced with warfarin. One year later, her visual function and optic fundus remain normal.

Case 2 was a 20-year-old man who reported two isolated painless episodes of TMVL in his OS. The first episode lasted 30 minutes, the second 4 hours. Both episodes were described as a “cloud over my OD.”

He was examined during the second episode of TMVL, at which time visual acuity was 20/20 OD and
20/70 OS. He had a trace relative afferent pupillary defect OS. Ophthalmoscopic examination showed isolated retinal venous engorgement OS. A few hours later, visual acuity spontaneously returned to normal.

Four days later, visual function and pupillary examination were normal. Ophthalmoscopy OS now showed two retinal flame hemorrhages in addition to the previously noted venous dilation (Fig. 2). Aspirin 325 mg/d was initiated.

An extensive coagulation workup was negative (4). Brain and orbital magnetic resonance imaging and magnetic resonance angiography of the neck and brain were normal. The patient’s visual function remained normal and there were no further TMVL episodes after a 6-month follow-up.

Our two patients experienced recurrent TMVL in the setting of dilated retinal veins as the only sign of a future CRVO that became ophthalmoscopically evident within 2 weeks of the initial symptom.

The most common symptom of CRVO is acute and persistent monocular visual loss. Recurrent episodes of TMVL are occasionally described by patients, but are usually associated with the classic full-blown ophthalmoscopic appearance of CRVO, including scattered intraretinal hemorrhages (1,2). We previously reported a patient with isolated dilated retinal veins and recurrent TMVL lasting 2 to 4 hours (3) who had typical ophthalmoscopic signs of CRVO 3 weeks later and was found to have hyperhomocystinemia (4).

Several characteristics of the TMVL should alert physicians to the diagnosis of a venous rather than an arterial cause. In the two cases we report here, and in our previously reported case, the TMVL episodes lasted 2 to 4 hours, longer than is typical for transient arterial retinal ischemia. TMVL from retinal arterial ischemia usually lasts no longer than 3 minutes (1). Also, our three patients described cloudiness of vision rather than the complete black-out of vision typical caused by arterial ischemia (1). Two of our patients mentioned positive visual phenomena (scintillations), which may signify a lower degree of retinal ischemia associated with slow venous flow (1).

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REFERENCES
Ocular Pathology, Fifth Edition

Myron Yanoff, MD and Ben S. Fine, MD. Mosby, St. Louis, 2002. ISBN: 0-323-01403-8, $259.00

Scope: This is a 761-page fifth edition of a classic originally published in 1975. The textbook seamlessly approaches the organizational level of a single-authored text without redundancy. It is divided into 18 chapters. Nine chapters detail tissue specific abnormalities (skin and lacrimal gland, conjunctiva, cornea and sclera, uvea, lens, neurosensory retina, vitreous, optic nerve, orbit). Five chapters cover disease entities (hereditary retinal dystrophy, diabetes mellitus, glaucoma, ocular melanotic tumors, retinoblastoma, and pseudoglioma). Four chapters cover general principles and processes (basic principles of pathology, nongranulomatous inflammation, granulomatous inflammation, and surgical and nonsurgical trauma).

The textbook is published as a single volume with 1685 of 1885 illustrations in color. These consist of photomicrographs, electron micrographs, gross photographs, facial, slit lamp and funduscopic photographs, illustrative schematics, and neuroradiographic images. As in previous editions, the material is presented in an expanded outline form rather than as traditional narrative text. There are multiple cross-citations to more complete discussions elsewhere, with references and recommended reading at the end of each chapter. "Clinical pearls" are interspersed throughout each chapter. The work is also available in CD ROM format.

The foreword, contributed by Morton E. Smith, MD, describes an intended audience of residents and fellows studying ophthalmology and pathology, as well as clinical practitioners of ophthalmology and diagnostic pathology.

Strengths: The authors contribute a beautiful collection of clinical, gross pathologic and histopathologic photographs, a testament to their years of experience, expertise, and understanding of pathophysiologic principles. It far surpasses collections in other clinical atlases. Cases come from the best of the Verhoeff Society, the Eastern Ophthalmic Pathology Society, published articles, and individual private collections. Common and rare entities are discussed and illustrated in detail not easily matched. The overall organization and cataloguing is comprehensive. The organization in outline form with interspersed clinical wisdom is well-suited to factual quick reference as well as web-based or multi-media learning systems. Clearly, the authors have produced a work easily adaptable to CD-ROM format.

Weaknesses: The cross-cited format makes for choppy reading. In the photomicrographs, the authors tend to under-label specific areas of interest, perhaps assuming more knowledge of pathology than most readers will have. By adding clinical presentations, signs, and symptoms, as well as pathophysiologic principles and clinical pearls to each entity, the authors are obliged to limit discussion of pathologic and histopathologic information.

It is sometimes difficult to work from a microscopic appearance toward an appropriate tissue diagnosis. For instance, if one had identified an orbital neoplasm as a "small blue cell tumor or a fibrous tumor of the orbit," it would be difficult to work backwards to develop a differential diagnosis and design further studies to refine the diagnosis.

Recommended Audience: Advanced students or clinical practitioners with an academic interest in clinical pathologic correlation will value this treatise.

Critical Appraisal: The textbook is an invaluable reference source and primary resource for the student or practitioner of ophthalmology and the general pathologist learning ophthalmology. The text does not easily serve the student looking for clues to pattern recognition and pattern-specific differential diagnosis.

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Ophthalmic Histopathology, 2nd Edition


Scope: This is a comprehensive single-authored illustrated textbook presenting an overview of ophthalmic pathology. The first chapter details the handling of specimens, from the instruments used for grossing specimens to use of special stains. Methods for documentation are shown, and the normal eye is reviewed.

Subsequent chapters are organized from the perspective of how specimens may be received in the laboratory. The initial eight chapters deal with the eye as a whole, in different disease settings: trauma, tumor, glaucoma, inflammation, vascular disease, retinal detachment, malformations, and the eye in systemic disease. The last five chapters cover specific anatomic parts of the eye and its adnexal or neighboring tissues: the eyelid, temporal artery, lacrimal sac, conjunctiva, orbit, cornea, and lens.

Illustrations (including color) are plentiful and of high quality. There are plenty of examples of special stains.
There is an abundance of gross specimens in addition to the usual microscopic photographs.

**Strengths:** The amount and quality of illustrations makes for better understanding of this very visual field. The completeness of information and unique organization of chapters also contributes to this being an excellent and usable reference.

**Weaknesses:** Finding a specific disease within a chapter requires that the reader leaf through much material or rely on the index. A table of contents at the beginning of each chapter would have helped.

**Recommended Audience:** This is a text for pathologists who work with the eye and pathology residents studying the eye. It is an unconventional reference for the ophthalmologist, but one that is easy to use and worth a serious look.

**Critical Appraisal:** This is one of the best basic texts of ocular pathology. It would make a welcome addition in any residency’s library.

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**Weiner & Levitt’s Pediatric Neurology, 4th Edition**

Michael E. Cohen, MD, Patricia K. Duffner, MD.  

**Scope:** This book is designed to guide medical students, interns, and residents in the recognition and therapy of pediatric neurologic disease.

The book is organized into some introductory chapters discussing basic concepts in neuroanatomy, history-taking, and physical examination. These are followed by descriptions of common presentations and management of pediatric neurologic diseases. Each chapter begins with a very brief clinical case presentation. Appendices cover basic concepts such as developmental milestones, head circumference for age, APGAR scoring, and the Glasgow Coma scale.

**Strengths:** Brief and uncluttered descriptions of diseases processes and their differential diagnoses are presented in outline form. Each chapter has a short but excellent reference section.

**Weaknesses:** There are errors in the neuro-ophthalmology presented in several chapters. For example, in chapter 2 (neuroanatomy), the lateral geniculate nucleus is described as part of the pupillary pathway. In chapter 4, (neurologic examination), the authors describe the ptosis of Horner syndrome as sometimes covering more than half of the pupil. In addition, the authors’ description of the Marcus-Gunn pupil misleadingly suggests a specific disorder of the papillomacular bundle. Also, there is a description of the tumbling “E” test for assessing visual acuity with a reference to a non-existent figure.

Further, the authors point out relative preservation of color vision in amblyopia, yet suggest that “optic atrophy” is present. A brief section on nystagmus suggests disorders of the medial longitudinal fasciculus are associated with “conversion retraction nystagmus,” a combination of a misspelling and a false association. In addition, the chapter on childhood myasthenia gravis makes no mention of the importance of the possible development of amblyopia.

**Recommended Audience:** Medical students, interns, and residents in pediatric medicine will find this book useful. They will be able to find disorders and their chief features quickly with appropriate references.

**Critical Appraisal:** The book’s problem oriented approach will be useful to the house officer. Unfortunately, careful inspection from a neuro-ophthalmologist’s perspective reveals errors that need to be corrected in forthcoming editions.

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**Contemporary Treatments in Neurology**


**Scope:** This is a collection of treatment-oriented deliberations, the stated purpose of which is to assist the busy neurologist who is “under pressure to keep up with the latest findings.” Neil Scolding, the editor of this synopsis, combines current, novel, and future therapeutic approaches with a discussion of recent treatment advances and an objective assessment of their impact.

The first chapter is a curious beginning for the book’s stated objective, entitled, “Important issues in the design, analysis and interpretation of clinical trials in neurology.” Peter Rothwell summarizes the importance of randomized controlled trials in a logical, clear, readable format. The principles outlined are not specific to neurologic science and do not connect to the central theme or body of the text. It is as if an important (and very well prepared) appendix to a major neurologic textbook had somehow lost its way and wound up here.

The remaining 19 chapters, written by 31 international (non-American) authors, are set in five major divisions:
degenerative diseases of the nervous system, inflammatory diseases, acquired and inherited metabolic disease, vascular diseases of the central nervous system, and episodic neurologic disease. Each very well referenced chapter begins with an introduction. The internal arrangement of individual chapters is idiosyncratic. The chapters, therefore, stand as interesting yet different excursions.

**Strengths:** Several chapters add background for treatment approaches by discussing mechanisms and pathophysiology. The quality of writing and use of language is consistently excellent. Inflammatory peripheral nerve disease (written by John Winer, University Hospital Birmingham, UK) is perhaps the most excellent chapter in the book. Diabetic peripheral nerve disease is described deftly by P. K. Thomas (Queen Square, London). There are substantial and somewhat surprising disparities in the continental approach compared with my American experience. For example, for treatment of orthostatic hypotension, fludrocortisone is recommended after "simple measures," yet midodrine hydrochloride (ProAmatine) is not mentioned.

**Weaknesses:** The major neurologic subspecialties, vascular disease, epilepsy, and neuro-muscular disorders, are well represented. The exception, disappointingly, is neuro-ophthalmologic syndromes. The chapter on multiple sclerosis (written by Alasdair Coles, Addenbrooke's Hospital, Cambridge, UK) begins the treatment portion with "symptomatic treatment." Tizanidine is described as "reputed to be less sedating," an assertion that experienced clinicians will question. If you are looking for helpful suggestions for difficult common symptoms, such as tremor and fatigue, they are not to be found here. Treatment of tremor is described as "rarely effective," and treatment of fatigue "remains both poorly understood and difficult." For acute relapses, there is heavy reliance on the Optic Neuritis Treatment Trial. This chapter, however, may contain the sole presentation of things neuro-ophthalmologic.

**Recommended Audience:** The recommended audience includes postgraduate trainees and practicing neurologists.

**Critical Appraisal:** The description of standard treatment here is unusual enough to suggest a somewhat different and decidedly European perspective and experience. This in itself makes for interesting reading. The lack of a consistent format across the numerous chapters adds an element of surprise. The work as a whole is quite readable, and interesting facts are sprinkled throughout. The first chapter is simply a gem, one that belongs in another work. This is a very readable text, but one that is neither as easy to use nor as current as a practicing American neurologist will expect.

**Stroke Prevention**


**Scope:** This is a small and easily readable text about the prevention of stroke, divided into sections on primary prevention, secondary prevention, and a section on transferring principles into practice. It is written by experts in the field of cerebrovascular disease and is intended for any practitioner responsible for altering patients' behavioral and medical risk factors. Typical stroke risk factors are examined, including non-modifiable and modifiable factors such as lipids, hypertension, and atrial fibrillation. Next, the text delves into more obscure risk factors such as alcohol consumption and the role of hormone treatment, and their influence on cerebrovascular disease. The second part of the book deals with secondary stroke prevention. There are chapters on cardiac anomalies, a discussion on the best dosage of aspirin, and the role of carotid endarterectomy, angioplasty, and stenting. The last section of the text discusses adapting information into clinical practice. There is an excellent chapter on the cost-effectiveness of stroke prevention.

**Strengths:** This text brings a wide number of studies under one cover, allowing one to review the myriad papers that have been presented elsewhere. All of the chapters are well written and cover many topics. The especially fine chapter on alcohol and stroke discusses the studies of stroke in relation to abstinence, moderate consumption, and heavy consumption. The chapter on hormone therapy examines stroke risk and hormone replacement, as well as the use of oral contraceptives, and discusses the merits and pitfalls of many of the studies. There is also a very thoughtful chapter on the cost-effectiveness of stroke prevention.

**Weaknesses:** Any book attempting to cover a subject that is so constantly changing suffers from the inevitability that some of its information will be out of date. For example, the chapter on cardiac anomalies does not include any data from the recent WARSS study (the book predates the release of that data); the chapter on secondary stroke prevention hedges on the exact dosage of aspirin to use.

**Recommended Audience:** This book is not so much for the clinician who sees many stroke patients as it is for the clinician who does not. As such, it will be helpful and beneficial to neuro-ophthalmologists.

**Critical Appraisal:** As a text that contains a review and synthesis of pertinent work from recent literature on the most important aspects of stroke prevention, it is worthwhile reading.

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The Molecular and Genetic Basis of Neurologic and Psychiatric Disease, 3rd Edition


Scope: This book provides a survey of the rapidly growing field of the genetics and molecular pathogenesis of neurologic and psychiatric disease. It is organized into three main sections. The first section deals with general categories of genetic disorders, the second section deals with neurologic disease, and the third section deals with psychiatric disease.

The section devoted to a general overview discusses basic concepts of genetics and inheritance. The basic mechanisms include triplet repeat disorders, prion disease, the various types of inheritance, degenerative disease, and proteins. There is also a chapter on genetically engineered models and their usefulness in research. The human genome project, gene mapping, the possibility of gene treatment, the models and their usefulness in research. The human genome project has been greatly expanded. In recent years many new loci for neurologic degenerative disease have been discovered and the gene map has been enlarged. The chapters now include Down syndrome as a classic genetic disorder, triplet repeat disease (genetics, clinical features, and pathogenesis), and prion disease. Mitochondrial disorders now comprise four chapters, one on the genome itself, a second on mutations in the mitochondrial genome, a third on mutations in the nuclear genome, and fourth on the role of mitochondria in neurodegenerative disorders. Other chapters concern the peroxisomal, lysosomal, and degenerative disorders, neurology, epilepsy, demyelinating disease, neuropathies, myopathies, dermatologic and brain disorders, lipoprotein and metabolic disorders, purines, porphyrias, metal metabolism, and vitamins.

A new addition to the book is the section on psychiatric disorders. There are chapters on genetic aspects of depression, bipolar disease, schizophrenia, obsessive compulsive disorder, addictions, and autism.

Strengths: The general organization of this book is very helpful in that the basic modern concepts of genetic disorders and their broad categories are discussed together, providing an overview of major dimensions of the field.

Among the major strengths of the book are its illustrations, diagrams, and charts. There are numerous black and white photographs of patients. The charts group diseases within a category or show relationships between these diseases. The diagrams indicate pathophysiology and show genetic sequences or the genome. The center has a section of color plates showing pathologic material and protein structures. A neurologic gene map is included.

Weaknesses: One of the weaknesses of the book is the brevity of the discussion of clinical features. That said, this book is an excellent complement to a clinical textbook or other clinical materials. Leber hereditary optic neuropathy (LHON), Kearns–Sayre syndrome (KSS), and the syndrome of neurotrophic ataxia, and retinitis pigmentosa (NARP) are discussed in just a few sentences. But these diseases are clearly shown in their context instead of in isolation, so one can see where neuro-ophthalmological findings fit into the context of broader manifestations of genetic diseases of the nervous system. The non–neuro-ophthalmologic features of these diseases are properly highlighted.

Recommended Audience: This book will be useful as a complement to more clinically oriented textbooks and papers. Clinicians will find an organized presentation of the basic facts along with suggestions as to where treatment might lie in the future. The authors should succeed in capturing the interest of the next generation of neurologists, psychiatrists, and neuroscientists.

Critical Appraisal: This book is rather unique: in one readable volume it reviews the basic categories of neurogenetic disease, their pathophysiology, and neurochemistry. The charts, diagrams, and photographs are useful. The organization is logical.

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Mergers of Teaching Hospitals in Boston, New York, and Northern California


Scope: John Kastor was chair of the department of Medicine at the University of Maryland for many years. Although his initial love was cardiac arrhythmias, his interest moved on to more global issues in academic medicine. His book is the product of his search to find the answers to the question, why are so many of the major teaching hospitals of our academic health centers merging? This is a wonderful history of three wonderfully researched vignettes of major teaching hospital mergers: that of the
Massachusetts General and Brigham and Women's Hospitals, Columbia Presbyterian and New York Hospitals, and Stanford and University of California San Francisco Hospitals. The book is written from the perspective of an investigative journalist and medical sociologist. It begins with an introduction to the environment of academic health centers and introduces the characters to be later discussed. Two chapters have been devoted to each of the three mergers. In first of these paired chapters, background forces and events that led to each merger are presented. In the second, Kastor relates what happened afterward. A final chapter summarizes what he learned and what these mergers can teach us.

Strengths: Its strengths are the quality and depth of research and detail, the clarity of writing and presentation, and the compelling interest of the stories and the people themselves. There are many familiar players, including ophthalmologists Bruce Spivey and Jackson Coleman and neurologists Flint Beall and Steve Hauser.

The overriding concern of the business of academic medical centers is painfully apparent in this monograph. MBAs trump the MDs every time, and yet when mergers succeed, it is the doctors who make it so. The book itself is a wonderfully honest, thoughtful, cogent analysis of one methodology used by academic health centers to improve their profitability and enhance their futures. These are three wonderful case studies that will be repeated elsewhere.

Weaknesses: There is little to be critical of here. Text, style, footnotes, and frequent subheading assist the reader through a maze of events and multiple characters.

Recommended Audience: This wonderful history will be of interest to those who go to hospitals, and to those who know and love hospitals. It will become required reading in business schools and it should become required reading in medical schools.

Critical Appraisal: This is a deeply researched, detailed, riveting piece of scholarship. It brings together several outstanding groups' common interests and struggles in the problematic industry that is hospital care. It makes real the relationships between deans and their CEOs, medical schools, and teaching hospitals.

The author offers insight into the conventional wisdom behind institutional mergers and exposes the strategic thinking of faculties, deans, and CEOs. It seems to suggest that there are no experts out there who really know what to do, and suggests that the mantra “bigger is better” may not actually hold for health care. It is a testament to the complexity and irrationality of the health care industry, and the talented business people who often leave their judgment at the door when they enter the health care arena.

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It was back to the slopes of Copper Mountain, Colorado, for the 31st Annual Meeting of the North American Neuro-Ophthalmology Society (NANOS). A total of 289 participants shuttled to the 10,000-feet base camp, with 26 arriving from abroad (Australia 7, Israel 5, Japan 5, Switzerland 4, France, Germany, Mexico, Lithuania, and Saudi Arabia, 1 each). A record-breaking 56 residents/fellows/medical students came.

As usual, the first day was devoted to the Frank B. Walsh Session, organized by the formidable neuro-ophthalmology team from the University of Pennsylvania, led by Nicholas Volpe, MD (Philadelphia). Also from the University of Pennsylvania were Lucy Rorke-Adams, MD, our guest neuropathologist, and Robert A. Zimmerman, MD, our guest neuroradiologist, who enriched the case material with their own collection of stained sections and unusual magnetic resonance images. The intrepid front row sages, apparently undaunted by the thin air, called out most of the answers (well, maybe not all of them). The rest of us were again stumped by the bizarre stories and twisted images generated by the 20 cases selected for presentation.

Kevin M. Barrett, MD, a resident in neurology at the Mayo Clinic, Jacksonville, Florida, received the award for the best Walsh Session paper by a resident or fellow for his presentation entitled “An Obvious Case of Giant Cell Arteritis.” It proved NOT to be giant cell arteritis at all, of course, but systemic amyloidosis that looked like giant cell arteritis in causing jaw claudication, limb girdle aches, transient monocular visual loss, fatigue, fever, and a high sedimentation rate. Temporal artery biopsy was negative but renal biopsy eventually gave the answer.

In keeping with the whodunit tradition of the Walsh meeting, all case answers, discussions, and references were withheld until the end of the Walsh session, when they were made available in the meeting book. The pathologic and imaging materials related to the case presentations were condensed onto a CDROM and given to each participant.

Extending over the next 3.5 days, the NANOS meeting included symposia on headache, featuring special guests Peter Goadsby, MD (London, England) and Judy C. Lane, MD (Denver, CO), “hot topics,” and pediatric neuro-ophthalmology, 22 platform presentations, 87 posters, and special tutorials on practice management and on the Neuro-Ophthalmology Virtual Education Library (NOVEL) being developed at the University of Utah.

Christopher Rodarte, BA, Columbia University, New York, received the award for the best presentation by a medical student for his platform talk entitled “A Quantitative Approach to Identifying Delayed Latencies in the Multifocal Visual Evoked Potential.” Clare Fraser, MBBS,
Waki Fujie, MD, PhD (Tokyo, Japan) and Kiran K. Vallam, MD, neuro-ophthalmology fellow at Michigan State University, in front of Dr. Vallam’s poster.

Kathleen B. Digre, MD (Salt Lake City, UT) and Gabrielle R. Bonhomme, MD, neuro-ophthalmology fellow at the University of Pennsylvania, and winner of best NANOS presentation by a fellow, at the resident/fellow reception.

Mark J. Kupersmith, MD (New York, NY), Steven Galetta, MD (Philadelphia, PA), and Larry Frohman, MD (Newark, New Jersey), NANOS President, take time out.

John B. Kerrison, MD (Baltimore, MD) explaining his poster in front of a balding presence (guess who?). From the back on the left is John L. Keltn, MD (Sacramento, CA). On the far right is Thomas M. Bosley, MD (Riyadh, Saudi Arabia).

William F. Hoyt, MD (San Francisco, CA) points out something important about the imaging of a third cranial nerve palsy associated with infliximab therapy on a poster by Michael S. Lee, MD (Cleveland, OH), et al. Standing by are Cameron F. Parsa, MD (Baltimore, MD) and colleague.

Joel M. Weinstein, MD (Madison, WI), Klara Landau, MD (Zurich, Switzerland), and Gabriela Wirth Barben, MD (St. Gallen, Switzerland) at the posters.

Nicholas J. Volpe, MD (Philadelphia, PA), chief organizer of the Walsh Session, with Emily DeCarlo, a medical student at the University of Pennsylvania, at his right, and Richard L. Sogg, MD (Palo Alto, CA) at her right.

Andrew Lee, MD (Iowa City, IA), Anthony C. Arnold, MD (Los Angeles, CA), and Bo Yang, MD (New York, NY), an about-to-be ophthalmology resident at the University of Iowa, at the resident/fellow reception.
Louis F. Dell Osso, PhD (Cleveland, OH) explains his concepts of what makes eyes wiggle to Rosa A. Tang, MD (Houston, TX) and Jason J. S. Barton, MD (Vancouver, BC).

Save Sight Institute, Sydney Eye Hospital, Sydney, Australia, received the award for the best presentation by a resident for her platform talk entitled “Multifocal Visual Evoked Potentials in the Differential Diagnosis of Acute Optic Neuritis.” Gabrielle R. Bonhomme, MD, Department of Neurology, University of Pennsylvania, received the award for the best presentation by a fellow for her platform talk entitled “Isolated Pediatric Optic Neuritis: Brain MRI Abnormalities and Risk of Multiple Sclerosis.” Steven F. Stasheff, MD, PhD, Children’s Hospital & Beth Israel-Deaconess Medical Center, Boston, Massachusetts, received the Tom & Susan Carlow Young Investigator Award for his paper entitled “Alterations in Spontaneous and Light-Evoked Ganglion Cell Activity During Retinal Degeneration in rd1 Mice.”

At the closing banquet, Steven E. Feldon, MD, MBA was honored for his enduring dedication to NANOS in receiving the Distinguished Service Award. Creig Hoyt, MD, was recognized as having been selected to give the 2004 William F. Hoyt Lecture at the Annual Meeting of the American Academy of Ophthalmology. His lecture, entitled “What We Do Not Know About Amblyopia,” will be published in the September 2005 issue of the Journal of Neuro-Ophthalmology.

The following society members were inducted as NANOS fellows: Valérie Biousse, MD (Atlanta, GA), Bradley K. Farris, MD (Salt Lake City, UT), Robert A. Egan, MD (Portland, OR), Mark Gans, MD (Montreal, PQ), Louise A. Mawn, MD (Nashville, TN), Thomas J. Mehelas, MD (Toledo, OH), Roger E. Turbin, MD (Newark, NJ), Agnes M. F. Wong, MD PhD, FRCSC (Toronto, ON), and Ruth Hun-Baron, MD (Tel Aviv, Israel) (international fellow).

The 2006 NANOS meeting will be held at the Starr Pass Marriott Resort and Spa, Tucson, Arizona from February 26 to March 2. The Walsh Session, organized by Shirley Wray, MD (Boston, MA) and Simmons Lessell (Boston, MA), will again occur on the first day. The 2007 NANOS meeting will be at the Snowbird Ski and Summer Resort, Snowbird, Utah from February 9 to 16. The 2008 NANOS meeting will be at the Renaissance Orlando Hotel at Sea World, Orlando, Florida from March 7 to March 13. The 2009 meeting will be in the cold, site and date to be announced. The 2010 meeting will be back at the Starr Pass Marriott Resort and Spa, Tucson, Arizona from February 27 to March 4.

Jonathan D. Trobe, MD
Ann Arbor, Michigan
Progress on the Neuro-Ophthalmology Virtual Education Library (NOVEL)

At the 2005 North American Neuro-Ophthalmology Society (NANOS) meeting at Copper Mountain, Colorado, librarians Valeri Craigle, MLS (Salt Lake City, UT) and Nancy Lombardo, MLS (Salt Lake City, UT) demonstrated that significant progress has been made on the Neuro-Ophthalmology Virtual Education Library (NOVEL) project. Anyone can access this freely available educational resource at http://library.med.utah.edu/NOVEL/. The NOVEL Updates page, located at http://medstat.med.utah.edu/NOVEL/NOVEL_Updates/index.html, provides the most recent information about the project and includes links to PowerPoint presentations and informational handouts with instructions on how to use the materials.

An important development is the incorporation of the Core Curriculum Outline for Neuro-Ophthalmology, created by Valerie Biousse, MD (Atlanta, GA) and the NANOS Curriculum Committee. The outline has been an invaluable resource for structuring the subject matter in each of the NOVEL collections. Ultimately, the curriculum outline will serve as a subject-based discovery tool that will link to all of the materials in NOVEL.

Contributions to NOVEL are welcomed and encouraged. Those who contribute to NOVEL will retain the copyright to their materials. For those wishing to submit their materials, an online contribution form is available on the Web site at http://library.med.utah.edu/NOVEL/contribute.html. All materials will be peer-reviewed before publication.

To make the materials valuable to the clinical practitioner, NOVEL has added descriptors such as anatomy, pathology, disease and diagnosis, and clinical symptoms and signs. Called metadata, it has been developed according to internationally recognized standards. Adhering to these standards allows NOVEL resources to be shared across systems and institutions.

At this time there are six collections available for use. The William F. Hoyt collection, which contains 855 slides, focuses on the optic disc and has been peer-reviewed by members of the NANOS Web Education Committee. The Shirley H. Wray collection holds approximately 100 patient case videos, with a potential total of 300 cases. This material was collected by Dr. Wray during her tenure as Director of Neurovisual Disorders at the Massachusetts General Hospital. The Moran Eye Center is a growing collection, and includes eye movement disorder videos collected by Kathleen B. Digre, MD (Salt Lake City, UT) and Daniel Jacobson, MD (deceased). It also includes video covering ophthalmoscopy and the neuro-ophthalmic examination. There is one outstanding video capturing an ongoing central retinal artery occlusion. The J. Lawton Smith collection consists of 87 lectures delivered by J. Lawton Smith, MD (Miami, FL) in the 1970s. The lectures are in MP3 audio format. Dr. Smith’s...
The William F. Hoyt Neuro-Ophthalmology Collection

This collection is part of the NOVEL project

Enter the Collection


large slide collection will also be added to NOVEL. The AAO-NANOS Clinical Collection is derived directly from the AAO-NANOS Clinical Neuro-Ophthalmology collection produced on CD. The 405 images are of selected cases from the NANOS teaching slide exchange, and the CD was produced under the direction of Larry Frohman, MD (Newark, NJ) and Andrew Lee, MD (Iowa City, IA). Future collections for NOVEL include the David G. Cogan Collection of video and slides and the cases presented at the annual Walsh Meeting.

The NOVEL team recognizes the value of collecting, preserving, and sharing these valuable materials. As source materials are acquired, each item is converted to digital form, cataloged, and uploaded to a database on the Web. Each collection is customized for the author yet maintains a similar layout and navigation scheme, which creates a sense of continuity and originality across the resource.

When obtaining materials for lectures, presentations, or for clinical research, users should be aware of the techniques for downloading the various media types and their appropriate use. Images are available in two formats; JPEG and TIF. The JPEG is quite sufficient for use in PowerPoint lectures, presentations, and Web pages. Choose the TIF if you want an image at its highest resolution and best quality. Be aware that the TIF images are large files, ranging from 10 to 24 megabytes in size. Files this size can take several minutes to download on slow Internet connections. Videos come in five formats, including two streaming formats and three download formats. A streaming file is appropriate for use only on the Web, not for downloading to your computer. You can link out to a streaming video file from a Web page or PowerPoint lecture.

The downloadable video files should be used only from the desktop or played from a CD. These files are approximately 100 megabytes—too large to use on the Web. Videos must be downloaded to the desktop for use in a PowerPoint lecture. The Windows Media download file is the only video format that can be used to embed into a PowerPoint presentation.

For further information, contact nancyl@lib.med.utah.edu or vcranigle@lib.med.utah.edu at the Spencer S. Eccles Health Sciences Library, 10 North 1900 East, Salt Lake City, Utah 84112.

Nancy T. Lombardo, MLS
Valeri Craigle, MLS
Spencer S. Eccles Health Sciences Library
University of Utah
Salt Lake City, Utah
## Upcoming Meetings

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Location</th>
<th>Contact Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>June 14–18, 2005</td>
<td>Canadian Congress of Neurological Sciences Annual Meeting</td>
<td>Ottawa, Ontario, Canada</td>
<td><a href="http://www.ccns.org/ccns_information/events.html">website</a></td>
</tr>
<tr>
<td>June 18–22, 2005</td>
<td>15th Meeting of the European Neurological Society</td>
<td>Vienna, Austria</td>
<td><a href="http://www.ensinfo.com">website</a></td>
</tr>
<tr>
<td>June 23–25, 2005</td>
<td>47th Annual Scientific Meeting of the American Headache Society</td>
<td>Philadelphia, Pennsylvania</td>
<td><a href="http://ahsnet.org/calendar/philly05">website</a></td>
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<tr>
<td>June 25–28, 2005</td>
<td>8th European Congress of Neuropathology</td>
<td>Amsterdam, Netherlands</td>
<td><a href="http://www.euro-cns.org/2005/">website</a></td>
</tr>
<tr>
<td>June 26–June 29, 2005</td>
<td>European Neuro-Ophthalmological Society (EUNOS)</td>
<td>Moscow, Russia</td>
<td><a href="http://www.nsi.ru/events/eunos/">website</a></td>
</tr>
<tr>
<td>July 26–28, 2005</td>
<td>28th Annual Meeting of the Japan Neuroscience Society</td>
<td>Yokohama, Japan</td>
<td><a href="http://www.congre.co.jp/neurosci2005/eng/info.html">website</a></td>
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<tr>
<td>September 17–20, 2005</td>
<td>9th Congress of the European Federation of Neurological Societies</td>
<td>Athens, Greece</td>
<td><a href="http://www.kenes.com/efns2005">website</a></td>
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<tr>
<td>September 25–28, 2005</td>
<td>130th Annual Meeting of the American Neurological Association</td>
<td>San Diego, California</td>
<td><a href="http://www.aneuroa.org/sf_prelim.html">website</a></td>
</tr>
<tr>
<td>September 25–29, 2005</td>
<td>Joint Meeting</td>
<td>Berlin, Germany</td>
<td><a href="http://www.soe2005.org">website</a></td>
</tr>
<tr>
<td>October 5–8, 2005</td>
<td>European Association for Vision and Research (EVER)</td>
<td>Vilamoura, Portugal</td>
<td><a href="http://www.ever.be">website</a></td>
</tr>
<tr>
<td>October 8–13, 2005</td>
<td>Congress of Neurological Surgeons 55th Annual Meeting</td>
<td>Boston, Massachusetts</td>
<td><a href="http://www.neurosurgeon.org/meetings/2005/index.asp">website</a></td>
</tr>
<tr>
<td>October 15–18, 2005</td>
<td>Annual Meeting of the American Academy of Ophthalmology (AAO)</td>
<td>Chicago, Illinois</td>
<td><a href="http://www.aoa.org/aaq/annual_meeting/">website</a></td>
</tr>
<tr>
<td>November 5–11, 2005</td>
<td>XVIII World Congress of Neurology</td>
<td>Sydney, Australia</td>
<td><a href="http://www.wcn2005.com">website</a></td>
</tr>
<tr>
<td>November 11–12, 2005</td>
<td>42nd Annual Meeting for the Japanese Neuro-Ophthalmological Society</td>
<td>Beppu-city, Oita, Japan</td>
<td>Contact: 97-549-4411 (Dr. Masatoshi Ishijima)</td>
</tr>
</tbody>
</table>
November 12–16, 2005
35th Annual Meeting of the Society for Neuroscience
Washington, DC
http://web.sfn.org/AM2004Splash.cfm
Contact: info@sfn.org

February 16–18, 2006
International Stroke Conference
Kissimmee, Florida
http://strokeconference.americanheart.org/portal/
strokeconference/sc/
Contact: strokeconference@heart.org

February 20–24, 2006
World Ophthalmology Congress
XXX International Congress of Ophthalmology
XVI Panamerican Congress of Ophthalmology
XVII Brazilian Congress of Prevention of Blindness
Sao Paulo, Brazil
http://www.ophthalmology2006.com.br/
Contact: info@ophthalmology2006.com.br

February 25–March 3, 2006
Tucson, Arizona
http://www.nanosweb.org/meetings/nanos2006/
Contact: ekunsey@nanosweb.org

March 15–19, 2006
American Association of Pediatric Ophthalmology & Strabismus (AAPOS) Annual Meeting
Keystone, Colorado
http://www.aapos.org/futuremeet.htm
Contact: aapos@aao.org

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

April 22–27, 2006
American Association of Neurological Surgeons Annual Meeting
San Francisco, California
http://www.aans.org/annual/2005/past_future_meetings.asp
Contact: info@aans.org

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

May 17–20, 2006
15th European Stroke Conference
Brussels, Belgium
http://www.eurostroke.org/esc_congresses.htm
Contact: Henrici@eurostroke.org

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

July 2–8, 2006
11th International Congress on Neuromuscular Diseases
Istanbul, Turkey
http://www.icnmd2006istanbul.org
Contact: icnmd2006@flaptour.com.tr

July 8–12, 2006
5th Forum of European Neuroscience
Vienna, Austria
http://fens2006.neurosciences.asso.fr/
Contact: christiane.riedl@uibk.ac.at

July 12–15, 2006
17th International Perimetric Society Meeting
Portland, Oregon
http://webeye.ophth.uiowa.edu/ips/meetings.htm

October 29–November 3, 2006
XVII International Congress of Eye Research
Buenos Aires, Argentina
http://www.icer2006.com/
Contact: http://www.icer2006.com/

November 29–December 2, 2006
XVI International Neuro-Ophthalmology Society Meeting (INOS)
Tokyo, Japan
http://www.inos2006.jp/
Contact: inos@inouye-eye.or.jp
ERRATUM

In the March 2005 issue of this journal, Kalapesi et al incorrectly stated that “...the third (postganglionic) (sympathetic) neuron passes from the superior cervical ganglion to the pupil, the LPS muscle, blood vessels of the eye and face, and the sweat glands of the face.” (JNO 2005; 25:7). The phrase should read: “...the third (postganglionic) (sympathetic) neuron passes from the superior cervical ganglion to the pupil, Mutter’s muscle, blood vessels of the eye and face, and the sweat glands of the face.”

Instructions for Authors appear in the March issue or online at www.jneuro-ophthalmology.com