EDITORIAL
161 Intravitreal Triamcinolone or Bevacizumab for Nonarteritic Anterior Ischemic Optic Neuropathy: Do They Merit Further Study?  
Shalom E. Kelman

ORIGINAL CONTRIBUTIONS
164 Intravitreal Triamcinolone Improves Recovery of Visual Acuity in Nonarteritic Anterior Ischemic Optic Neuropathy  
Berkant Kaderli, Remzi Aavi, Ali Yucel, Kazim Guler, and Oner Gelisken

169 Bilateral Isolated Lateral Geniculate Body Lesions in a Patient With Pancreatitis and Microangiopathy  
Raghu Mudumbai and Anuja Bhandari

176 Peripapillary Nerve Fiber Layer Thickness Measured by Optical Coherence Tomography in Patients With No Light Perception From Long-Standing Nonglaucomatous Optic Neuropathies  
Carmen K. M. Chan and Neil R. Miller

180 Optic Disc Edema, Cystoid Macular Edema, and Elevated Vascular Endothelial Growth Factor in a Patient With POEMS Syndrome  
Deborah Y. Chong, Grant M. Comer, and Jonathan D. Trobe

184 Choroidal and Optic Nerve Infarction in Hepatitis C-Association Polyarteritis Nodosa  
Yanina Kostina-O’Neil, Guy V. Jirawuthiworavong, David N. Podell, and Robert L. Lesser

189 Primary Sinonasal Undifferentiated Carcinoma Presenting With Bilateral Retrobulbar Optic Neuropathy  
Madhura A. Tamhankar, Nicholas J. Volpe, Laurie A. Loewner, James N. Palmer, and Michael Feldman

PHOTO ESSAY
193 Terson Syndrome With Bilateral Optic Nerve Sheath Hemorrhage  
Chiaki D. Gauntt, Richard G. Sherry, and Chithra Kannan

STATE OF THE ART
195 Intrinsically Photosensitive Retinal Ganglion Cells  
Aki Kawasaki and Randy H. Kardon

205 Efficacy of Corticosteroids and External Beam Radiation in the Management of Moderate to Severe Thyroid Eye Disease  
Christopher I. Zoumalan, Kimberly P. Cockerham, Roger E. Turbin, Nicholas J. Volpe, Michael Kazim, Raymond S. Douglas, and Steven E. Feldon for
Contents (continued)

215 Thrombolysis for Central Retinal Artery Occlusion
    Valérie Biousse, Olivier Calvetti, Beau B. Bruce, and Nancy J. Newman

231 Joel Glaser: A Scholar’s Scholar
    Jonathan D. Trobe

238 Treatment of Nonarteritic Anterior Ischemic Optic Neuropathy With Intravitreal Bevacizumab
    Jeffrey L. Bennett, Scott Thomas, Jeffrey L. Olson, and Naresh Mandava

240 Central Retinal Vein Occlusion as a Possible Presenting Manifestation of Sneddon Syndrome
    Tina Aggermann, Paulina Haas, and Susanne Binder

241 Angiographic Shaded Surface Display Artifact Falsely Suggests Ophthalmic Artery Stenosis
    Maria Woodward, Nancy J. Newman, and Valérie Biousse

242 Retinal Migraine
    Frederick E. Lepore

243 Retinal Migraine
    Seymour Solomon, Brian M. Grosberg, Deborah I. Friedman, and Richard B. Lipton

244 Authors’ Reply
    Valérie Biousse and Nancy J. Newman

BOOK REVIEWS

246 Adams and Victor’s Principles of Neurology, 8th Edition
    Valérie Biousse

246 Fundamentals of Neurologic Disease
    Dean M. Cestari

246 Localization in Clinical Neurology, 5th Edition
    Jonathan D. Trobe

247 Cranial Nerves: Functional Anatomy
    Nancy J. Newman

248 Clinical Neuropathology: Text and Color Atlas
    Jonathan D. Trobe

248 Neurology and Trauma, 2nd Edition
    Luis M. Tumialán

249 Digital Neuroanatomy: An Interactive CD Atlas With Text
    Beau B. Bruce

ERRATA

In the June 2007 issue of the journal, the report of the 33rd Annual Meeting of NANOS in Snowbird, Utah in February 2007 (J Neuroophthalmol 2007;27:155-8) omitted mention that Swaraj Bose, MD was a co-moderator of the symposium entitled “Novel Approaches to the Treatment of Neuro-Ophthalmic Diseases.”

In the article “Clinical Without Histopathological Manifestations of Inflammation in a Patient with Primary Intraorbital Optic Nerve Sheath Meningioma” (J Neuroophthalmol 2007;27:104-6) an author’s name was incorrectly spelled as Sureka Thiagalingham. It should have appeared as Sureka Thiagalingam.

Lippincott Williams & Wilkins cannot be held responsible for errors or for any consequences arising from the use of the information contained in this journal. The appearance of advertising in this journal does not constitute an endorsement or approval by Lippincott Williams & Wilkins of the quality or value of the product advertised or of the claims made for it by its manufacturer.

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

PERMISSION TO PHOTOCOPY ARTICLES: This publication is protected by copyright. Permission to photocopy must be secured in writing from: Permissions Dept., Lippincott Williams & Wilkins, 351 West Camden Street, Baltimore, MD 21201; FAX: 410-528-8550; or Copyright Clearance Center (CCC), 222 Rosewood Dr., Danvers, MA 01923; FAX: 978-750-4470; or UMI, Box 49, 300 North Zeeb Road, Ann Arbor, MI 48106-1346; FAX: 313-761-1203.

Manuscripts should be submitted to Mireille Prusak, Editorial Assistant of the Journal of Neuro-Ophthalmology, Kellogg Eye Center, Department of Ophthalmology, 1000 Wall Street, Ann Arbor, MI 48105.

Address for subscription information, orders, or changes of address (except Japan): 16522 Hunters Green Parkway, Hagerstown, MD 21740-2116, or call 1-800-638-3030, in Maryland call collect 301-714-2300. Subscribers requiring an address change must submit an old mailing label and their new address, including the zip code. No claims for copies lost in the mail can be allowed unless they are received within 90 days of the date of issue. Claims for issues lost as a result of insufficient notice of change of address will not be honoured.

Advertising inquiries should be directed to Renée Artuso, Lippincott Williams & Wilkins, 530 Walnut Street, Philadelphia, PA 19106-3621. Fax: (516) 741-2247.
Intravitreal Triamcinolone or Bevacizumab for Nonarteritic Anterior Ischemic Optic Neuropathy: Do They Merit Further Study?

Shalom E. Kelman, MD

Nonarteritic anterior ischemic optic neuropathy (NAION) remains a major cause of sudden loss of vision in elderly individuals. The results of the Ischemic Optic Neuropathy Compression Trial (IONDT) (1) demonstrated that optic nerve sheath decompression not only did not produce better visual outcomes than occurred in the non-intervention group but also was actually harmful. The study also defined for the first time the natural history of the disease. At 6 months, 42% of the patients in the nonintervention group experienced significant clinical improvement (doubling of the visual angle).

A most unexpected and important result of the IONDT was the determination of second eye involvement with NAION. Before the IONDT, reports had suggested that second eye involvement occurred in up to 45% of patients. The IONDT demonstrated a rate of close to 15% over 5 years (2). At the time of a first eye involvement with NAION when a terribly anxious patient asks “What will happen to my other eye?” we can now answer with confidence that the risk of involvement of the second eye is relatively low.

Even so, second eye involvement may render the patient visually disabled. Our sense of frustration and desperation with this subgroup of patients strongly motivates a search for new innovative treatments. Although there is much hope regarding the contribution of stem cells, the benefits of this approach are unlikely be realized for 20–30 years. We desire a treatment that we can use in the very near future.

In this issue of the Journal, Kaderli et al (3) report improved visual acuity and rapid reduction in optic disc edema after intravitreal injection of triamcinolone in 4 eyes of patients with NAION. Bennett et al (4) reported similarly impressive results in a single patient with NAION after intravitreal injection of bevacizumab. As pointed out by the authors of both reports, the small sample and lack of concurrent controls limit the conclusions. Nevertheless, small studies of this nature are hypothesis-generating and ought to serve as a stimulant to larger and better-designed trials.

Is there a plausible rationale for the benefit of either agent in NAION? Kaderli et al (3) propose that by reducing optic disc edema through corticosteroids, “the vicious cycle of ischemia, edema, and compartment syndrome” may be ameliorated. They also suggest that the corticosteroid anti-inflammatory effect may be beneficial on the basis of limited histopathologic data. Unfortunately, the science to support these hypotheses is weak. The pathophysiology of NAION remains poorly understood. There is very limited pathologic material available to determine whether there is an inflammatory component in NAION. Bennett et al (4) postulated that acute expression of vascular endothelial growth factor (VEGF) may cause harmful optic disc edema and pointed out that inhibition of VEGF signaling has reduced cerebral edema and tissue injury in a mouse stroke model.
Before we consider embarking on a large scale, expensive clinical trial using one or the other of these agents in NAION, it is worth recalling the process we went through in generating the IONDT, of which I was the lead investigator.

In the late 1980s, optic nerve sheath decompression for NAION seemed to work but the rationale was weak. In 1987, I visited Robert Sergott, MD, in Philadelphia to observe his performance of optic nerve sheath decompression surgery on 2 patients with papilledema from idiopathic intracranial hypertension (pseudotumor cerebri). In 1988, Dr. Sergott and his colleagues published favorable results with use of this procedure in the management of papilledema (5). I soon started performing the procedure, and after achieving successful outcomes in many patients with papilledema, I became a strong advocate.

In 1989, Sergott et al (6) published the lead article in Archives of Ophthalmology showing that 12 of 14 patients with progressive NAION (characterized by reported worsening over at least 7 days) improved after undergoing optic nerve sheath decompression, whereas only 1 of 3 patients with sudden, nonprogressive visual loss improved after this type of surgery. They noted that in a control group with nonprogressive NAION, only 2 of 15 eyes demonstrated spontaneous improvement. They concluded that optic nerve sheath decompression benefited patients with progressive NAION but not those with acute, nonprogressive NAION.

After reading this report, Michael Elman, MD, a retinal surgeon with a strong background in clinical trial design, and I began to offer the procedure to selected patients with NAION. We published our favorable results in a group of 7 patients (7), cautioning that the natural history was still unknown and suggesting that the improvement was not limited to the progressive form of NAION.

Dr. Elman and I took our idea of a multicenter randomized trial of optic nerve sheath decompression in NAION to Dr. Sergott in recognition of his pivotal role in applying optic nerve sheath decompression to NAION. He declined to participate, stating that he lacked the clinical equipoise necessary to proceed with a randomized clinical trial. He believed that the literature supported his impression that spontaneous improvement was very rare and that his experience with the procedure demonstrated significant rates of improvement. Under the circumstances, he could not ethically submit his patients to random trial assignment.

We developed a plan that would ultimately lead to funding for a multicenter clinical trial. Letters were sent to neuro-ophthalmologists requesting that they perform chart reviews of their patients with NAION. Based on these chart reviews, we were able to arrive at an estimate of the spontaneous improvement rate and the prevalence of the disease. Power calculations could now be performed, and we arrived at an estimate of the number of patients we would need to demonstrate a statistically significant effect of treatment.

As a result of these chart reviews, we suspected that the natural history was better than had been reported and that the published reports were not rigorous. During the 1990 American Academy of Ophthalmology meeting in Atlanta, Dr. Elman and I locked ourselves in our hotel rooms to write a National Eye Institute (NEI) grant proposal. At that meeting, I engaged in a heated debate with Sohan S. Hayreh, MD, who animately asserted that the scientific rationale for sheath decompression was flawed. (He later published his opposition to the rationale for surgery in NAION in a letter to the editor [8]). Despite being disheartened by the rebuke of one of the world’s leading authorities on NAION, we continued our work.

We were propelled by a sense that a clinical trial undertaken soon after sheath decompression was gaining popularity would be the most effective way to prevent dissemination of a potentially harmful intervention. The NEI accepted our proposal on the first try, an almost miraculous occurrence. Our hard work and preparation had paid off, but the truly difficult part of running a clinical trial had just begun.

Twenty-five clinical centers were selected and training began. Surgeons studied videotapes on the surgical procedure, clinical coordinators received training in vision testing, and a manual of operations was developed. Eventually the clinical centers were certified and up and running, and our first patient was enrolled in October of 1992, a short 34 months after optic nerve sheath decompression was first reported as a treatment for NAION. Enrollment was highly successful. But within 24 months of entering the first patient, the Data and Safety Monitoring Committee halted the study after 244 patients had been randomly assigned. The data had demonstrated that surgery was not beneficial and perhaps harmful, even in patients with progressive disease. Most unexpectedly, the natural history arm demonstrated improvement of vision in 42% of patients who had not undergone surgery at 6 months (1). Subsequent follow-up in the second phase of the study demonstrated a 5-year rate of second eye involvement of only 15% (2). As noted by Leonard Levin, MD, in an accompanying editorial to the initial report (9), “the barn door was closed in time.”

What are the implications of the IONDT for another multicenter clinical treatment trial of NAION? Power calculations can now be carried out with better precision based on the IONDT data. These calculations depend on the expected magnitude of the treatment effect relative to the spontaneous improvement rate. Given the relative large spontaneous improvement rate found in the IONDT, much larger numbers of patients will be needed to demonstrate a modest effect of a new intervention. On the other hand, if the intervention is expected to produce a dramatic improvement in function, fewer patients will be needed.
The magnitude of the effect that intravitreal triamcinolone or bevacizumab has on visual outcomes will determine the feasibility of the study. If the results of the small studies of intravitreal triamcinolone or bevacizumab reported here are reproducible and the magnitude of improved visual acuity and rapidity of resolution of the disc edema can be substantiated in further pilot studies, then power calculations may demonstrate the feasibility of a multicenter clinical treatment trial.

One important difference between then and now is the possibility of testing these interventions in an animal model. The rodent model (10,11) and, more recently, the primate model of NAION (12) have been developed to the point that putative interventions such as intravitreal corticosteroid or anti-VEGF injections can be tested before human trials are begun. This approach would not unduly delay the introduction of a promising new treatment. On the other hand, if animal models fail to demonstrate any potential benefit, patients will be spared another clinical trial with negative results.

REFERENCES

1. The Ischemic Optic Neuropathy Decompression Trial Research Group. Optic nerve decompression surgery for nonarteritic anterior ischemic optic neuropathy (NAION) is not effective and may be harmful. JAMA 1995;273:625–32.
Intravitreal Triamcinolone Improves Recovery of Visual Acuity in Nonarteritic Anterior Ischemic Optic Neuropathy

Berkant Kaderli, MD, Remzi Avci, MD, Ali Yucel, MD, Kazim Guler, MD and Oner Gelisken, MD

Background: The visual outcome in untreated nonarteritic anterior ischemic optic neuropathy (NAION) is dismal. Because intravitreal triamcinolone (IVTA) has shown promise in improving edematous retinal disorders, a pilot trial of this therapy in NAION was considered reasonable.

Methods: Four eyes of 4 patients with severe visual loss due to NAION were treated with 4 mg IVTA (study group). The control group consisted of 6 consecutive patients with NAION who received no treatment. Patients were evaluated by the visual acuity and visual field measurements of the Early Treatment Diabetic Retinopathy Study (ETDRS) and fluorescein angiography.

Results: All patients completed at least 9 months of follow-up. In the study group, the mean improvement in visual acuity were 4, 5.8, and 6.2 ETDRS lines at the first and third weeks and final visit, respectively. Optic disc swelling and leakage had markedly decreased at the first postinjection week and had disappeared by the third week examination in all eyes. In the control group, the mean improvements in visual acuity were 0, 0.7, and 1.3 ETDRS lines at the first and third weeks and final visit, respectively. Control eyes showed resolution of the optic disc swelling between the fourth week and third month visits. No marked change in visual field defects was observed in either group.

Conclusions: IVTA provided relatively improved recovery of visual acuity and relatively rapid resolution of optic disc swelling in a small sample of patients with acute NAION. It did not provide visual field improvement. A larger trial is merited by the results of this small pilot study.
The durations of visual loss before study entry were 22, 12, 10, and 10 days in Cases 1, 2, 3, and 4, respectively (Table 1). Automated visual field examination (Humphrey 30–2) disclosed nerve fiber bundle defects typical of NAION in affected eyes; visual fields were normal in fellow eyes. Optic disc edema and peripapillary hemorrhages were present in all affected eyes; the cup-to-disc ratio was 0.2 in all fellow eyes. Fluorescein angiography showed leakage in all affected optic discs. Neither ophthalmoscopy nor fluorescein angiography revealed diabetic macular edema in any eyes.

All patients had systemic hypertension with a duration of at least 5 years. Cases 1, 2, and 3 had type 2 diabetes mellitus with durations of 1, 10, and 5 years and hemoglobin A1C levels of 6.5, 7.3, and 6.9 mg/100 mL, respectively. Internal consultation revealed suboptimal blood pressure and moderate metabolic control of diabetes in all patients. Only Case 2 had signs of mild diabetic retinopathy without macular edema. Westergren erythrocyte sedimentation rate and serum reactive protein levels were normal in all patients. Neurologic consultations revealed no suspicion of multiple sclerosis or intracranial pressure increase.

Study group patients were informed of the natural course of NAION and of various suggested treatment modalities including periocular or systemic corticosteroids, aspirin, hyperbaric oxygen, topical brimonidine tartrate, and IVTA. After the aim of the study and the possible risks had been fully explained, they provided informed consent.

An intravitreal injection of 4 mg/0.1 mL triamcinolone (TA) was then performed in the affected eye of each of all 4 study group patients. The intravitreal injection was carried out in the outpatient department under sterile conditions with subconjunctival anesthesia. The injection was applied with a 27 gauge needle, 3.5 mm from the superior temporal or nasal limbus. The continuity of optic disc blood supply was confirmed with ophthalmoscopy immediately after the injection in all eyes. To prevent secondary ocular hypertension, all eyes received topical 0.2% brimonidine tartrate twice daily during the first postinjection month.

Outcomes were evaluated by Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity and automated visual field measurements and fluorescein angiography at the first and third weeks, third month, and every 3 months thereafter. We recorded potential complications such as a rise in intraocular pressure, cataract progression determined by slit-lamp biomicroscopy, and endophthalmitis.

**Control Group**

The control group consisted of 6 consecutive patients who presented to a private eye clinic from June 2004 to January 2005 and in whom NAION was diagnosed. Exclusion criteria were the same as those for the study group. The duration of visual loss before initial examination was 8, 14, 7, 18, 11, and 14 days in control Cases 1, 2, 3, 4, 5, and 6, respectively (Table 2). The Goldmann visual field examination disclosed nerve fiber bundle defects typical of NAION in affected eyes of all 6 control patients. Optic disc swelling and peripapillary hemorrhages were present in all affected eyes. The cup-to-disc ratio was 0.2 in all affected eyes of control patients. Fluorescein angiography showed leakage in all affected optic discs without signs of macular edema. All patients had systemic arterial hypertension with a duration of at least 8 years. Cases 2 and 4 had type 2 diabetes mellitus with durations of 10 and 11 years and hemoglobin A1C levels of 7.0 and 7.2 mg/mL, respectively. Internal consultation revealed optimal blood pressure and moderate metabolic control of diabetes in all patients. Both patients with diabetes had signs of mild diabetic retinopathy without macular edema. The Westergren erythrocyte sedimentation rates and serum reactive protein levels were normal for age in all patients. Neurologic consultations revealed no other abnormalities. All patients continued to receive their antihypertensive and antidiabetic drugs. All patients were given 150–300 mg aspirin daily. To reduce intraocular pressure, all eyes received 0.2% topical brimonidine tartrate (Cases 1, 5, and 6).

### TABLE 1. Case characteristics and visual results of the study group

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Duration of visual loss (days)</th>
<th>Type of visual field defect</th>
<th>Initial visual acuity</th>
<th>Postinjection visual acuity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>64/M</td>
<td>+/+$</td>
<td>10</td>
<td>Inferior altitudinal; inferotemporal arcuate</td>
<td>20/200</td>
<td>20/200 20/100 20/63 20/63 20/63 20/63</td>
</tr>
<tr>
<td>4</td>
<td>57/F</td>
<td>+/+$</td>
<td>22</td>
<td>Inferior altitudinal</td>
<td>20/800</td>
<td>20/500 20/400 20/400 20/400</td>
</tr>
<tr>
<td>1</td>
<td>67/F</td>
<td>+/+$</td>
<td>12</td>
<td>Superior altitudinal</td>
<td>20/500</td>
<td>20/80 20/63 20/63 20/63 20/63</td>
</tr>
<tr>
<td>2</td>
<td>58/M</td>
<td>+/-$</td>
<td>10</td>
<td>Superior altitudinal</td>
<td>20/200</td>
<td>20/80 20/40 20/32</td>
</tr>
<tr>
<td>3</td>
<td>57/F</td>
<td>+/+$</td>
<td>10</td>
<td>Inferior altitudinal</td>
<td>20/200</td>
<td>20/80 20/63 20/63 20/63 20/63</td>
</tr>
<tr>
<td>1</td>
<td>67/F</td>
<td>+/+$</td>
<td>12</td>
<td>Superior altitudinal</td>
<td>20/500</td>
<td>20/80 20/63 20/63 20/63 20/63</td>
</tr>
<tr>
<td>2</td>
<td>58/M</td>
<td>+/-$</td>
<td>10</td>
<td>Superior altitudinal</td>
<td>20/200</td>
<td>20/80 20/63 20/63 20/63 20/63</td>
</tr>
</tbody>
</table>

DM, diabetes mellitus; HT, systemic hypertension.
or 0.5% timolol maleate (Cases 2, 3, and 4) twice daily during the first 4 weeks.

The control patients were evaluated by visual acuity measurement with the ETDRS chart, Goldmann perimetry, ophthalmoscopy, and color fundus photographs at the initial visit, first and fourth weeks, third month, and every 3 months thereafter. Fluorescein angiography was performed only at the initial visit.

The approval of the ethics committee of our university was obtained for this study.

RESULTS

All study patients completed at least 12 months of follow-up. The mean improvements in visual acuity were 4, 5.8, and 6.2 ETDRS lines at the first and third weeks and final visit, respectively. Optic disc swelling and leakage markedly decreased during the first week and had disappeared by the third week examination in all cases (Fig. 1). The visual field mean deviations at baseline were 19.13, 20.97, 30.32, and 14.89 dB in study Cases 1, 2, 3, and 4, respectively. The corresponding numbers were 19.98, 14.16, 23.22, and 13.75 dB at the first and 20.39, 13.13, 18.47, and 12.31 dB at the third postinjection week. The typical visual field defects persisted in all study eyes. None of the patients showed deterioration of visual acuity or visual field or recurrence of optic disc edema during the follow-up period. All eyes eventually developed partial optic disc pallor. None of the eyes developed intraocular pressures exceeding 21 mm Hg, worsening cataract, or endophthalmitis.

All control patients completed at least 9 months of follow-up. The mean improvements in visual acuity were 0, 0.7, and 1.3 ETDRS lines at the first and third weeks and final visit, respectively (Table 2). Two control patients (Cases 2 and 5) showed 3 lines of visual improvement. All control eyes still had optic disc swelling at the fourth week visit. At the third month visit, only control Case 3 still had

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years) and gender</th>
<th>HT/DM</th>
<th>Duration of visual loss (days)</th>
<th>Type of visual field defect</th>
<th>Visual acuity Initial</th>
<th>1st week</th>
<th>4th week</th>
<th>Final</th>
<th>Visual acuity</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>67/F</td>
<td>+/−</td>
<td>8</td>
<td>Inferior altitudinal</td>
<td>20/200</td>
<td>20/320</td>
<td>20/200</td>
<td>20/200</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>70/M</td>
<td>+/+</td>
<td>14</td>
<td>Diffuse scotoma</td>
<td>20/800</td>
<td>20/800</td>
<td>20/400</td>
<td>20/400</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>74/M</td>
<td>+/−</td>
<td>7</td>
<td>Inferior altitudinal</td>
<td>20/200</td>
<td>20/200</td>
<td>20/250</td>
<td>20/200</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>56/F</td>
<td>+/+</td>
<td>18</td>
<td>Inferior altitudinal</td>
<td>20/200</td>
<td>20/125</td>
<td>20/125</td>
<td>20/100</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>68/M</td>
<td>+/−</td>
<td>11</td>
<td>Inferior altitudinal</td>
<td>20/200</td>
<td>20/200</td>
<td>20/200</td>
<td>20/100</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>68/F</td>
<td>+/−</td>
<td>14</td>
<td>Inferior altitudinal</td>
<td>20/320</td>
<td>20/320</td>
<td>20/320</td>
<td>20/250</td>
<td></td>
<td>9</td>
</tr>
</tbody>
</table>

DM, diabetes mellitus; HT, systemic hypertension.

FIG. 1. Retinal fluorescein angiography of Case 3. A. Initial visit angiogram of the right eye demonstrates diffuse leakage prominent in the upper half of the optic disc. B. Third week visit angiogram shows complete resolution of optic disc swelling and leakage. Visual acuity improved from 20/200 to 20/40.
Intravitreal Triamcinolone in NAION

partial optic disc swelling. Goldmann perimetry revealed no change in visual field defects in the control eyes. Partial optic disc pallor was eventually observed in all affected eyes in the control group.

**DISCUSSION**

All IVTA-injected eyes in this series showed a relatively favorable recovery of visual acuity and a relatively rapid resolution of optic disc edema. Visual acuity recovery of 5 ETDRS lines was observed in all patients except Case 1, who had no improvement. The NAION in this patient had been present for 22 days before study entry, a relatively long time in this cohort. Typical visual field defects persisted in all eyes.

The greatest visual improvement in our study group occurred at the first postinjection visit (mean, 4 ETDRS lines) and third post-injection visit (mean, 5.8 ETDRS lines). By contrast, in our control group, the greatest visual improvement (mean, 1.3 ETDRS lines) occurred at the final follow-up visit.

The discordance between the visual results of our control group and that of the Ischemic Optic Neuropathy Decompression Trial Study Group (6), in which 31% of untreated cases had an increase in 3 lines of vision at 24 months, can be attributed to the small sample in our study.

All IVTA-injected eyes showed a marked decrease in optic disc swelling and leakage during the first week after injection and disappearance of the edema by the third week visit. The optic disc edema in NAION has been reported to resolve spontaneously within 6–8 weeks (7,8). Notably, all 6 control patients in our study still had optic disc edema at the fourth week and all eyes except the eye of Case 3 showed resolution at the third month visit.

There is a rationale for the use of intravitreal corticosteroids in NAION. In NAION a vicious cycle of ischemia, edema, and compartment syndrome develops, leading to further tissue infarction. Neuroprotection cannot directly or solely resolve this vicious cycle (9), but reduction of optic disc edema could improve the reversible component of ischemic insult and blocked axoplasmic transport. Histopathologic studies performed in patients with brain infarction and ischemic optic neuropathy showed that the number of macrophages in the affected area increases over time (10). This response can negatively contribute to the axonal death process. Whether IVTA would work as it does in uveitic, pseudophakic, and diabetic macular edema and intraocular inflammation is unknown (11).

The only previous study of IVTA in NAION (12) produced negative results. In 3 patients with NAION who were treated with 20 mg IVTA, Jonas et al (12) reported that after a follow-up ranging between 3 and 5 months, visual acuity changed from 0.1 to 0.2 in 1 patient, from 0.5 to 0.2 in 1 patient, and from 0.16 to 0.2 in 1 patient. No major perimetric improvement was observed in any patients. The 20 mg dose used is much higher than the 4 mg dose we used. Moreover, they did not provide information about the duration of optic disc edema before treatment. These discrepancies make the comparison of the results of the two studies difficult. The higher the dose of IVTA, the longer it remains in the eye (13,14). Optic disc edema lasts for 6–8 weeks in NAION (6,7), a period short enough to be covered by 4 mg IVTA, the antiedematous effect of which lasts for at least 3 months in cases of diabetic macular edema (11,15). Therefore, extending the duration of the effect of IVTA by using higher doses does not seem necessary. Shields et al (16) reported uncontrolled results of 4 mg IVTA injections in 9 patients with radiation papillopathy. In their study, signs of optic neuropathy such as hyperemia and edema resolved, often within 1 month. Visual acuity was stable or improved in 7 patients. The mean time to improvement in visual acuity by ≥2 lines was 3 weeks. Over the mean of 11 months of follow-up, improvement or stabilization of visual acuity was noted in 7 of 9 patients. The authors believed that their intervention improved on the natural history of radiation papillopathy.

The interpretation of our results is cautioned by the small sample size. Randomized studies with larger sample sizes are needed to show safety and efficacy.

**REFERENCES**

2. The Ischemic Optic Neuropathy Decompression Trial Research Group. Optic nerve decompression surgery for nonarteritic anterior ischemic optic neuropathy (NAION) is not effective and may be harmful. *JAMA* 1995;273:625–32.


Bilateral Isolated Lateral Geniculate Body Lesions in a Patient With Pancreatitis and Microangiopathy

Raghu C. Mudumbai, MD and Anuja Bhandari, MD, FRCOphth

Abstract: An 18-year-old woman developed pancreatitis and a thrombotic microangiopathy but no electrolyte abnormalities. She required intubation hours after admission and was not able to communicate for 8 days. Upon recovering consciousness, she reported severely impaired vision in both eyes, but ophthalmologic evaluation and neuroimaging were not obtained until several days later. Ophthalmologic examination documented retinal infarcts and profound binocular vision loss with hourglass bilateral homonymous hemianopic visual field loss. MRI showed signal abnormalities restricted to the area of the lateral geniculate bodies (LGBs) with characteristics most suggestive of hemorrhagic infarction. Very few cases of isolated bilateral LGB lesions have been reported. Damage has been attributed to myelinolysis from osmotic demyelination or to infarction from microvascular occlusion. This case conforms more to microvascular infarction. The vulnerability of the LGB to selective microvascular infarction may be based on a combination of its unique architecture and high metabolic demand.


Acute bilateral lesions of the lateral geniculate bodies (LGBs) are rarely reported (1–8). Two major etiologies have been proposed: myelinolysis and ischemia. We present a patient who developed acute bilateral visual loss in the setting of acute pancreatitis and pathologically demonstrated renal microangiopathy. Brain imaging disclosed lesions confined to the LGBs with signal characteristics suggesting hemorrhagic infarction.

CASE REPORT

An 18-year-old woman developed acute pancreatitis and a microangiopathy. She denied alcohol abuse, mumps, or use of corticosteroids or other medications. She was taking oral contraceptive pills. She was admitted to a community hospital because of impaired consciousness, pulmonary edema, and hypoxemia and was intubated shortly after admission.

Serum calcium and triglyceride levels were normal, and results of abdominal ultrasound, and abdominal CT scans were negative. The serum amylase level was elevated at 4,836 U/L (normal 30–110 U/L). She had thrombocytopenia with a platelet count of 74,000/L (150,000–400,000/L) and anemia with a hematocrit of 28.4% (35%–46%). There was an increase in schistocytes. The lactate dehydrogenase (LDH) level was elevated at 11,874 U/L (313–618 U/L), results of a Coombs test were negative, the D-dimer level was >6,700 ng/mL (<500 ng/mL), haptoglobin was <7 mg/dL (37–308 mg/dL), and fibrinogen was 252 mg/dL (170–410 mg/dL). Thrombin time and prothrombin time were normal. Partial thromboplastin time (PTT) was mildly elevated at 54 seconds (23–36 seconds). The von Willebrand factor cleaving protease (ADAMTS-13) activity was mildly decreased at 59% (67%–177%), and the inhibitor level of 0.4% with subsequent testing revealed an activity level of 83%. An ADAMTS-13 level of <5% is consistent with congenital or idiopathic thrombotic thrombocytopenic purpura (TTP), but modest decreases, as seen in our patient, are found in a variety of conditions, including disseminated intravascular coagulation (DIC). Antinuclear antibody and antineutrophilic cytoplasmic antibody levels were normal. Initial renal parameters were elevated with a blood urea nitrogen (BUN) of 29 mg/dL and creatinine of 3.8 mg/dL, both of which steadily rose. The combination of falling platelets, prolonged PTT, minimal schistocytes, and significantly elevated D-dimer led to a provisional diagnosis of DIC due to pancreatitis.

Because of renal failure, she was treated with hemodialysis. A renal biopsy showed cortical infarction. There was arteriolar and arterial thrombosis and intimal thickening consistent with microangiopathy. Immunofluorescence revealed fibrin and vascular thrombi. These pathologic findings, together with the laboratory results, were consistent with a diagnosis of thrombotic microangiopathy (TMA).
Eight days into her illness, she was extubated and reported impaired vision such that she could not recognize faces. She was transferred 10 days after onset of initial symptoms to our facility for further evaluation and management of acute pancreatitis accompanied by acute renal failure and DIC.

The patient remained anuric and continued to undergo hemodialysis. Results of the following tests were all normal: activated protein C resistance, antiphospholipid antibody panel, protein S antigen, protein C activity, prothrombin DNA screen, antithrombin III, complement 3, and complement 4. At no time did the patient have hyponatremia or hypernatremia.

Brain MRI (Fig. 1), performed without contrast 11 days after the onset of symptoms and 3 days after the patient was capable of reporting visual impairment, revealed bilateral symmetrical FLAIR signal hyperintensities in the posterior thalami in the region of the LGBs. There was increased signal on T1 MRI suggestive of a hemorrhagic lesion. There was no restricted diffusion on diffusion imaging. A gradient echo MRI sequence was not performed. Precontrast brain CT scanning, performed 17 days after onset of symptoms and 9 days after the report of visual loss, showed no abnormalities. (A repeat scan performed 32 months later revealed the same increased signal on T1 MRI, suggesting a hemorrhagic lesion.)

Twelve days after her initial symptoms, our ophthalmologic examination performed in the eye clinic disclosed best-corrected visual acuities of 8/200 in both eyes. Color vision with Ishihara plates was 3/15 right eye and 0/15 left eye. In dim illumination, pupils were measured at 6 mm both eyes and reacted briskly to light. There was no afferent pupillary defect. Anterior segment examination was unremarkable. Dilated fundus examination was normal in the right eye. A few cotton-wool spots and a single retinal hemorrhage were noted along the superior vascular arcade in the left eye (Fig. 2). Goldmann visual field examination (Fig. 3) performed 12 days after the report of visual loss showed hourglass visual field defects in both eyes.

After our initial examination, the patient was treated with 250 mg intravenous methylprednisolone every 6 hours for 24 hours followed by a tapering dose of 60 mg prednisone with a 10 mg taper per day. During the course of her hospital stay, the pancreatitis improved with a decrease in amylase level to 440 U/L. At discharge, the platelet count was normal at 172,000/µL, hematocrit was normal at 22%, and creatinine was normal at 9.9 mg/dL.

On examination 32 months after illness onset, her best-corrected visual acuities were 20/25 right eye and 20/20 left eye. Color vision by Ishihara plates was 2/11 right eye and 2/11 left eye. The pupils reacted briskly. No afferent pupillary defect was present. There was more optic disc pallor in the left eye than in the right eye. Goldmann visual field examination (Fig. 4) showed slight improvement in the visual field loss.

**DISCUSSION**

Bilateral isolated LGB lesions, as seen in our patient, have been described rarely. (Table 1) The earliest report dates to 1933 when Mackenzie et al (1) described a case of syphilitic anterior choroidal arteritis resulting in bilateral LGB infarcts. In 1972, Merrcn (2) provided details of a 37-year-old woman with pancreatitis who was found on autopsy to have well-demarcated coagulative necrosis of both LGBs and hemorrhage of the right basis pontis in association with microangiopathic hemolytic anemia and renal necrosis. The patient was an alcoholic with a disputed history of methanol consumption.

In 1995, Donahue et al (7) presented a patient with hourglass visual field defects from bilateral LGB lesions attributed to central pontine myelinolysis after liver...
transplantation for alcoholic cirrhosis. In 1996, Greenfield et al (3) described a woman thought to have a “lateral geniculitis” in association with severe diarrhea. In 2001, Barton (6) described a patient with liver failure who underwent a liver transplant and had developed visual loss four months prior to neuro-ophthalmologic examination. She was believed to have extrapontine myelinolysis. In 2002, Moseman and Shelton (4) reported a woman with LGB and retinal infarctions from vasoconstriction in severe pre-eclampsia. In the same year, Imes et al (5) reported a patient thought to have intrageniculate myelinolysis affecting selective layers of the LGB (with sparing of the pons) after near fatal uterine hemorrhage requiring a hysterectomy. In 2004, Lefebvre et al (8) reported on a 31-year-old woman who had anaphylactic shock resulting in hemorrhagic infarcts of both LGBs.

Our patient, like the patient of Merren (2), developed pancreatitis with subsequent DIC, pulmonary edema, and renal failure. She was significantly hypotensive throughout much of her hospital course (low blood pressure of 89/41 mm Hg). Renal biopsy was consistent with a microangiopathy and renal thrombosis. ADAMTS-13 activity was only mildly low. (Severely decreased ADAMTS-13 activity is thought to be a marker for TTP)

A complaint of blurred vision led to our examination, which showed fresh retinal infarcts in one eye, hourglass bilateral homonymous hemianopia, and MRI revealing a normal-appearing brain except for FLAIR signal hyperintensities in LGBs with increased signal on T1 suggestive of blood products within the lesion. This clinical presentation led us to believe that the patient had bilateral hemorrhagic infarctions of the LGBs.

The LGB (9) is a cap-like structure on the posterior end of the thalamus. It has a very high metabolic rate and a dual blood supply, consisting of the anterior choroidal artery that arises from the internal carotid artery and supplies the anterior hilus and the lateral choroidal artery, a branch of the posterior cerebral artery that supplies the rest of the nucleus including the macular zone. The LGB has multiple layers of tightly connected, criss-crossing white and gray matter.

Myelinolysis, or osmotic demyelination, has been proposed in three reports (5-7) as the cause of bilateral LGB damage (Table 1). Myelinolysis usually occurs in individuals with chronic debilitating conditions such as alcoholism and liver disease after chronic hyponatremia has been rapidly reversed. Affected structures include the pons and various extrapontine sites such as the cerebellum, thalamus, caudate, putamen, and LGB. In the acute phase, MRI discloses symmetric hypointense signal on T1 and hyperintense signal on T2/FLAIR and may acutely show enhancement with contrast (10).

The LGB is thought to be affected because it shares the same grid arrangement of white and gray matter as the
pons, where there is tight meshing between neurons and oligodendroglia that makes these tissues sensitive to osmotic forces (11). Because of their compact relationship with surrounding neurons, the oligodendrocytes in the LGB and pons have a limited capacity to swell as a means of maintaining iso-osmolality with the extracellular space. They are then forced to actively extrude osmolytes, a process that leads to cell shrinkage.

**FIG. 4.** Goldmann visual field examination performed 32 months after the first report of visual loss shows some improvement relative to initial Goldmann visual field values.

<table>
<thead>
<tr>
<th>Study</th>
<th>Age</th>
<th>Sex</th>
<th>Visual field defects</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mackenzie et al&lt;sup&gt;1&lt;/sup&gt;</td>
<td>N/A</td>
<td>F</td>
<td>Incongruous symmetric superior altitudinal hemianopia and lower nasal quadrant defect OD</td>
<td>N/A</td>
</tr>
<tr>
<td>Merren&lt;sup&gt;2&lt;/sup&gt; 1972</td>
<td>37</td>
<td>F</td>
<td>Unable – Light perception vision</td>
<td>N/A</td>
</tr>
<tr>
<td>Donahue et al&lt;sup&gt;7&lt;/sup&gt; 1995</td>
<td>37</td>
<td>F</td>
<td>Bilateral congruous hourglass defects</td>
<td>Initial: Increased T2 signal in central pons with sparing of peripheral pons; F/U: T2 high signal of LGBs 6 months later</td>
</tr>
<tr>
<td>Greenfield et al&lt;sup&gt;3&lt;/sup&gt; 1996</td>
<td>28</td>
<td>F</td>
<td>Left homonymous wedge- shaped defects and incongruous right homonymous hemianopia</td>
<td>Increased T2 signal of LGBs and left optic tract. Minimal enhancement</td>
</tr>
<tr>
<td>Imes et al&lt;sup&gt;5&lt;/sup&gt; 2002</td>
<td>33</td>
<td>F</td>
<td>Bilateral, highly incongruous sectoranope defects</td>
<td>Symmetrically decreased T1 signal with enhancement, increased T2/FLAIR signal of LGBs and optic tracts</td>
</tr>
<tr>
<td>Moseman and Shelton&lt;sup&gt;4&lt;/sup&gt; 2002</td>
<td>21</td>
<td>F</td>
<td>Unable (Light perception only)</td>
<td>Symmetric, bilateral decreased T1 signal, increased FLAIR/T2 signal in LGBs</td>
</tr>
<tr>
<td>Lefèbvre et al&lt;sup&gt;8&lt;/sup&gt; 2004</td>
<td>31</td>
<td>F</td>
<td>Incongruous binasal and bitemporal defects improving over time</td>
<td>Symmetric lesions of LGBs and parahippocampal regions seen on FLAIR as high signal intensity suggestive of hemorrhagic ischemia. Normal T1 without enhancement. Hemosiderin on gradient echo imaging</td>
</tr>
</tbody>
</table>

N/A, not available.
Of the three patients in whom LGB lesions were attributed to myelinolysis, the patient reported by Donahue et al (7) presents the most convincing scenario. This was a young woman with alcoholic cirrhosis and chronic hyponatremia who was undergoing liver transplantation. She underwent overcorrection of serum sodium to hypernatremia; she did not have hypotension or severe blood loss. Increased T2 MRI signal was present in the central pons with sparing of the peripheral pons. Repeat MRI months later, using Horton’s (12) protocol for imaging the LGB, disclosed hyperintense lesions in both LGBs on T2 MRI. The patient of Imes et al (5) had a clinical course complicated by massive hemorrhage and hypotension requiring hysterectomy; there was no hyponatremia. The patient of Barton et al (6) had mild hyponatremia before hepatic transplant and mild hyponatremia postoperatively and did not have “excessive hypotension or blood loss.” LGB lesions were alleged on the basis of hourglass visual field defects, but MRI performed 5 months after the transplant showed only a small left lateral thalamic T2 hyperintensity. CT scanning performed 13 days after transplantation was normal, and there is no mention of MRI performed at that time.

The patient of Barton et al (6), although not having clear vasculopathic confounders, does require postulation of purely extrapontine myelinolysis with relatively minor sodium osmolality shifts and without radiologic support of bilateral LGB involvement. The patient of Imes et al (5) may have had LGB infarction related to the severe hemorrhage and hypotension instead of the proposed myelinolysis.

As an alternative to myelinolysis, vascular compromise by a variety of mechanisms has been proposed as the mechanism of bilateral LGB lesions (1,2,4,8). Mackenzie et al (1) provided histopathologic evidence of syphilitic gumma and arteritis of the anterior choroidal arteries in a single case of bilateral LGB damage. In discussing why

<table>
<thead>
<tr>
<th>Timing of MRI from presentation</th>
<th>Associated findings</th>
<th>Proposed etiology</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td>Prior right hemiparesis and left hemibody paresthesias that resolved completely</td>
<td>Syphilitic arteritis</td>
<td>LGBs infiltrated by syphilitic gummas, also present in thalamus</td>
</tr>
<tr>
<td>N/A</td>
<td>Pancreatitis; renal failure</td>
<td>Microangiopathy; ? methanol toxicity</td>
<td>LGB: coagulative necrosis; Kidney: patchy areas of coagulative necrosis + reactive glomerulitis Blood: schistocytes c/w microangiopathic hemolytic anemia</td>
</tr>
<tr>
<td>2 weeks</td>
<td>Alcoholic cirrhosis; chronic hyponatremia; post-operative encephalopathy</td>
<td>Central pontine myelinolysis; hyponatremia corrected; no systemic hypotension</td>
<td>None</td>
</tr>
<tr>
<td>1 week</td>
<td>Diarrhea</td>
<td>“Lateral geniculitis” temporally related to infectious etiology of diarrhea</td>
<td>None</td>
</tr>
<tr>
<td>Not stated</td>
<td>Hypotensive Respiratory distress</td>
<td>“Intrageniculate myelinolysis” after near fatal uterine hemorrhage and hysterectomy</td>
<td>None</td>
</tr>
<tr>
<td>1 day</td>
<td>Retinal ischemia</td>
<td>Preeclampsia, eclampsia, vasoconstriction</td>
<td>None</td>
</tr>
<tr>
<td>1 day</td>
<td>Anaphylactic shock; Systemic hypotension</td>
<td>Ischemia of LGB</td>
<td>None</td>
</tr>
</tbody>
</table>
the anterior choroidal arteries should be affected in isolation, he stated that syphilis can symmetrically affect any part of the body, including the hands, iris, and choroid. The patient of Merren (2), like ours, had pancreatitis and a microangiopathy that led to renal failure. Despite the fact that the LGB has a dual arterial circulation, Merren (2) postulated that if acute arterial compromise occurred quickly, necrosis would occur before anastomoses could become effective. He also noted that the microangiopathic process led to occlusion of small arterioles that could cause infarction in the kidneys and the LGBs. His theory was supported by pathologic evidence of liquefactive necrosis in the LGBs.

In refuting the notion that myelinolysis accounted for LGB damage in their patient, Lefebvre et al (8) pointed out that the hemorrhage seen on MRI, which had not been noted in any reported cases of myelinolysis, probably resulted from disruption of the blood-brain barrier in the distribution of the anterior and lateral posterior choroidal arteries. They attributed the lack of restricted diffusion to the fact that 16 days had elapsed between the onset of visual loss and performance of MRI. In their patient, the low signal of hemosiderin deposits was still seen on gradient echo MRI 1 year later. They hypothesized that hemorrhagic infarction had damaged the LGBs and suggested that the LGBs lay in watershed zones.

The mechanism of LGB damage in our patient is also more likely to have been small vessel occlusive disease with hemorrhagic infarction rather than myelinolysis. There was strong evidence of a thrombotic microangiopathy and no evidence of rapid osmotic shifts. We acknowledge that if these were fresh hemorrhagic infarctions, we would have expected to find restricted diffusion on diffusion imaging and high signal attenuation on brain CT scanning. Like Lefebvre et al (8), we attribute the lack of restricted diffusion on diffusion imaging to the fact that the MRI was performed 11 days after our patient's coma began. Given that the patient's consciousness had been impaired, we do not know how long the LGB damage was present before she was even able to notice visual loss. Restricted diffusion is known to dissipate within 10–14 days of vascular compromise (13). The absence of signal attenuation on fresh blood on the brain CT could be explained by the even greater delay from the first report of visual loss to the performance of the CT scan and the fact that the area of the putative hemorrhage is very small.

As further support for the mechanism of vascular occlusion in our patient, she had features of TTP and hemolytic uremic syndrome (HUS), two microangiopathies that lead to platelet microthrombi, which can occlude arterioles and capillaries (14). The overlap between TTP and HUS has led to their being considered forms of TMA. Renal failure and neurologic abnormalities are common features. Cerebral microthrombi can be seen in 50% of HUS cases going to autopsy with evidence that cerebral and renal endothelial cells may share susceptibility to apoptosis from TTP/HUS (15,16). DIC, a known complication of severe pancreatitis, could easily have accounted for the microvascular occlusions (17,18). Moreover, both acute pancreatitis and DIC have been associated with acute bilateral renal necrosis (19).

Our patient is strikingly similar to the patient of Merren (2), who also had pancreatitis and developed abnormalities of coagulation that led to TMA and LGB lesions. Pathologic evaluation of the LGBs in the Merren's patient (2) showed clear evidence of ischemic necrosis rather than myelinolysis.

Myelinolysis and ischemia each provide adequate pathophysiologic mechanisms for LGB damage, but they do not provide a satisfying explanation as to why the LGBs should have been compromised without apparent damage to other parts of the central nervous system. The hypothesis of Lefebvre et al (8) that the LGB is part of a watershed zone is tenuous because of the infrequent involvement of the LGB in other watershed infarcts. Myelinolysis most typically involves the pons with less frequent involvement of other structures like the LGB.

The high metabolic demand of the LGBs may make them vulnerable to myelinolysis or ischemic damage. Myelinolysis usually requires hypernatremia from rapid correction of chronic hyponatremia leading to extravasation of intracellular fluid to the intravascular space, which results in rapid dehydration of the oligodendrocytes. If isotonicity is not established before inorganic ion shifts occur, cells must synthesize organic osmotes to prevent further cell shrinkage. If the metabolic rate is high enough, patients with poor nutrition become at risk for the development of demyelination because they cannot easily generate the compensatory organic osmotes (11).

The vulnerability of the LGB to infarction might also be based on its vascular architecture. Fujino (20) found that blood vessels ran vertically through the LGB, from which short transverse vessels branched off. Each vertical vessel gave branches to corresponding laminae. Importantly, there were no anastomoses between the cellular layers of the LGB and between the LGB and optic radiations. The most vascular areas of the LGB were the intermediate quadrant (macula) and the caudal portion. The blood supply to the medial and lateral quadrants was relatively poor. The small clusters of terminal capillaries did not have overlap in their vascular supply. Fujino (20) concluded that "this rich vascularity points to the active metabolism which must be taking place in this important structure." Also, "with the rich vascularity of the macular region of the LGB, it would be difficult for a small vascular accident to affect macular function severely. Because each vertical vessel sends branches..."
to corresponding areas of adjoining laminae, an occlusion of one of these vessels would result in a homonymous field defect. And because of the lesser vascularity of the quadrants representing peripheral visual fields, occlusion of these vessels would result in a relatively large field defect.”

It is interesting that every reported case of bilateral LGB lesions has involved women, particularly during pregnancy. TTP/HUS is associated with pregnancy and has a preponderance in women. A meta-analysis of 2,229 patients with TTP/HUS showed that 66% were women and that 13% of 837 women with TTP/HUS were pregnant (21).

Acknowledgments

We thank Drs. Kenneth Maravilla (Radiology) and John Harlan (Hematology) at the University of Washington, Dr. Louis Sokoloff at the National Institute of Health, and Dr. Marcus Raitche at Washington University for their comments regarding metabolism in the brain and lateral geniculate bodies, and Dr. Phillip P. Chen at the University of Washington for his review of the manuscript.

REFERENCES

Peripapillary Nerve Fiber Layer Thickness Measured by Optical Coherence Tomography in Patients With No Light Perception From Long-Standing Nonglaucomatous Optic Neuropathies

Carmen K. M. Chan, MRCP, MRCOphth and Neil R. Miller, MD

Background: The residual peripapillary retinal nerve fiber layer thickness (PRNFLT) corresponding to no light perception vision from long-standing nonglaucomatous optic neuropathies has not been documented. Such a benchmark would be useful information because PRNFLT is being used as an indicator of the visual recovery potential in patients with optic neuropathies.

Methods: By means of optical coherence tomography (OCT) using a fast RNFL thickness protocol, we determined the PRNFLT in 8 patients with no light perception (NLP) for at least 1 year from acquired nonglaucomatous optic neuropathies. All patients underwent an assessment of visual acuity, color vision, visual field, pupillary reactions to light stimulation, and ophthalmoscopy.

Results: Four of the 8 patients had a normal fellow eye. The average PRNFLT in the 4 normal eyes was 97.90 μm (range 94.82–100.89 μm), whereas the average PRNFLT in 8 of the 9 eyes with NLP was 45.42 μm (range 37.65–51.46 μm).

Conclusions: Eyes with long-standing NLP vision from nonglaucomatous optic neuropathies retain a residual PRNFLT of about 45 μm as measured by OCT. This should be taken into consideration when using PRNFLT to assess visual prognosis in patients with poor vision from various optic neuropathies.

(Optical coherence tomography (OCT) is a noninvasive method that has been used to assess macular and optic disc morphology as well as peripapillary retinal nerve fiber layer thickness (PRNFLT). In particular, some authors have recommended using PRNFLT to assess the potential for visual recovery in patients with optic neuritis (1). Theoretically, its use may also be extended to optic neuropathies from other causes, such as trauma and compression. Because OCT demonstrates anatomical structures quite well, many authors have attempted to correlate the thickness of the PRNFL with visual function. The normal average PRNFLT is age dependent (2) and is in the range of 98–104 μm as measured with the fast RNFL thickness function of the Stratus optical coherence tomograph (3,4). In eyes with impaired vision from optic neuropathy, the PRNFLT is reduced. For example, Trip et al (5) demonstrated that in 25 eyes with previous optic neuritis, with an average visual acuity of logMar +0.23 (Snellen equivalent 20/30), the average PRNFLT was 68.7 μm. Fisher et al (6) showed that in patients with multiple sclerosis and optic atrophy, visual function scores were linearly correlated with PRNFLT, in that for every 1 line decrease in low-contrast letter acuity or contrast sensitivity score, the mean PRNFLT decreased by 4 μm.

However, because the PRNFL not only contains visual axons but also supports glial cells and blood vessels, even complete optic nerve atrophy would not be expected to result in complete loss of the PRNFL as measured by OCT. Indeed, glia constitute at least 18% of the primate RNFL (7). OCT may be detecting the glial content together with the sheaths of dead axons thickened by gliosis. Glial proliferation was demonstrated in a histologic study of eyes blind from glaucoma (8). In addition, there may be persisting but nonfunctional retinal ganglion cell axons. In a histologic study of enucleated eyes blind from optic neuropathy, 24 (42%) of 57 eyes had residual axons numbering at least 5% of normal values (9). This issue is extremely important if one is going to use PRNFLT to predict the potential for visual recovery in patients with various optic neuropathies such as optic neuritis, trauma, or compression.)

as those caused by compression or trauma. Although a recent study reported that the average PRNFLT as determined with OCT in 17 eyes blind from glaucoma was 44.93 ± 4.95 μm (10), it is unclear whether this value is applicable to patients with nonglaucomatous optic neuropathies. In this study, we determined the minimal PRNFLT in eyes with no light perception (NLP) from long-standing nonglaucomatous optic neuropathies.

**METHODS**

This prospective study was conducted at the Neuro-ophthalmology Unit of the Wilmer Eye Institute, The Johns Hopkins Hospital, with institutional review board approval. Patients with NLP from an acquired nonglaucomatous lesion of one or both optic nerves were included in the study. Specifically, the duration of documented NLP had to be at least 1 year, and the patient had to have an absent pupillary reaction to direct light stimulation and no intraocular pathologic condition that could explain the visual acuity or affect the PRNFLT. Eight such patients were identified.

OCT was performed on both eyes of each patient using a Stratus optical coherence tomograph 3.0 (Carl Zeiss, Meditec, Dublin, CA) with software version 4.0.4. A fast RNFL thickness (3.4) scan acquisition protocol was used and the results were analyzed with the RNFL thickness average analysis (both eyes) function. In scanning the blind eye, the external fixation target was used to allow the patients

### TABLE 1. Baseline demographics of study patients with long-standing nonglaucomatous primary optic atrophy resulting in no light perception vision in at least one eye

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Cause of optic neuropathy</th>
<th>NLP eye</th>
<th>Duration of NLP (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>21</td>
<td>Optic nerve glioma, s/p radiotherapy</td>
<td>OS</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>34</td>
<td>Traumatic optic neuropathy*</td>
<td>OS*</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>40</td>
<td>Unknown (patient also has an optic neuropathy of unknown cause in the fellow eye)</td>
<td>OD</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>51</td>
<td>Spheno-orbital meningioma, s/p surgery and radiotherapy</td>
<td>OS</td>
<td>16</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>52</td>
<td>Optic neuritis and multiple sclerosis</td>
<td>OD</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>55</td>
<td>Spheno-orbital meningioma, s/p surgery</td>
<td>OS</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>72</td>
<td>Optic nerve sheath meningioma, s/p surgery</td>
<td>OD</td>
<td>14</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>73</td>
<td>Suprasellar meningioma, s/p surgery and radiotherapy</td>
<td>OD</td>
<td>14</td>
</tr>
</tbody>
</table>

*Case 2: Both eyes affected (NLP). We were unable to satisfactorily capture an OCT image from the right eye because of nystagmus.
NLP, no light perception; OCT, optical coherence tomography; OD, right eye; OS, left eye; s/p, status post.

### TABLE 2. Average PRNFLT in the 8 study eyes (with NLP) and fellow eyes

<table>
<thead>
<tr>
<th>Case</th>
<th>Average PRNFLT of NLP eye (μm)</th>
<th>Fellow eye normal?</th>
<th>Average PRNFLT of fellow eye (μm)</th>
<th>NLP eye PRNFLT (% of normal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45.74</td>
<td>Y</td>
<td>96.25</td>
<td>47.5</td>
</tr>
<tr>
<td>2</td>
<td>42.43</td>
<td>N</td>
<td>Unable to measure</td>
<td>Not applicable*</td>
</tr>
<tr>
<td>3</td>
<td>49.66</td>
<td>N</td>
<td>36.02</td>
<td>Not applicable*</td>
</tr>
<tr>
<td>4</td>
<td>37.65</td>
<td>Y</td>
<td>94.82</td>
<td>39.7</td>
</tr>
<tr>
<td>5</td>
<td>44.32</td>
<td>N</td>
<td>50.78</td>
<td>Not applicable*</td>
</tr>
<tr>
<td>6</td>
<td>51.46</td>
<td>Y</td>
<td>100.89</td>
<td>51.0</td>
</tr>
<tr>
<td>7</td>
<td>48.62</td>
<td>Y</td>
<td>99.62</td>
<td>48.8</td>
</tr>
<tr>
<td>8</td>
<td>43.49</td>
<td>N</td>
<td>56.15</td>
<td>Not applicable*</td>
</tr>
<tr>
<td>Average</td>
<td>45.42</td>
<td></td>
<td></td>
<td>46.8</td>
</tr>
</tbody>
</table>

*Not applicable as fellow eye was abnormal.
PRNFLT, peripapillary nerve fiber layer thickness; NLP, no light perception.
FIG. 1. Optical coherence tomography images of the right eye (normal) of Case 4, demonstrating the ISNT rule (inferior ≥ superior ≥ nasal ≥ temporal).

to fixate with their sighted fellow eye if necessary. A signal strength of at least 5 was achieved in all patients except Case 4 (see below) in whom the signal strength was compromised by an uneven cornea due to concurrent trigeminal and facial nerve palsy causing keratopathy, but the data acquisition was determined to be adequate for analysis.

FIG. 2. Optical coherence tomography images of Case 3. Visual acuity in the right eye is no light perception (NLP) and in the left eye is 20/200. Note that the peripapillary nerve fiber layer thickness is greater in the right eye (NLP eye) than in the left eye (20/200 eye). For a possible explanation, see text.
The visual function of the fellow eyes was determined by Snellen visual acuity at distance, Jaeger visual acuity at near, color vision using Hand-Rand-Rittler pseudoisochromatic plates, visual field examination using Humphrey perimetry, and ophthalmoscopy.

RESULTS

Baseline demographic data are summarized in Table 1 and the PRNFLT results are summarized in Table 2. The average PRNFLT of the 8 eyes with NLP was 45.42 \( \mu \text{m} \) (range 37.65–51.46 \( \mu \text{m} \)). The average PRNFLT of the 4 normal eyes was 97.90 \( \mu \text{m} \) (range 94.82–100.89 \( \mu \text{m} \)). For Case 3, a woman with bilateral optic neuropathy thought to be inflammatory or ischemic in origin, the PRNFLT was actually thicker in the NLP eye than in the fellow eye (which had 20/200 best-corrected visual acuity and inferior visual field loss). Normal eyes should show a characteristic configuration for disc rim thickness of inferior \( \approx \) superior \( \approx \) nasal \( \approx \) temporal, termed the ISNT rule (11) (Fig. 1).

In the 4 normal eyes in this study, the average PRNFLTs in the inferior, superior, nasal, and temporal quadrants were 126.0, 114.8, 86.8, and 64.0 \( \mu \text{m} \), respectively, obeying the ISNT rule. This pattern was lost in the 8 NLP eyes, which averaged PRNFLTs of 44.8, 52.5, 44.1, and 40.1 \( \mu \text{m} \) in those four quadrants, respectively.

DISCUSSION

This small case series demonstrates that the minimal average PRNFLT in eyes with NLP from long-standing, nonglaucomatous optic neuropathies is approximately 45 \( \mu \text{m} \), a figure consistent with the average PRNFLT of 44.93 \( \mu \text{m} \) found in glaucomatous blind eyes by Sihota et al (10). Three possible explanations exist as to why the PRNFLT thickness in such cases is 45%-50% of the average thickness in normal eyes. First, OCT may be detecting the glial content together with the sheaths of dead axons thickened by gliosis. Second, there may be persisting but nonfunctional retinal ganglion cell axons (9). It is possible that these residual retinal ganglion cells project to the pretectal nuclei/superior colliculus/hypothalamus and do not directly participate in the formation of visual images. Third, the residual thickness may be an artifact generated by the built-in software of the OCT.

None of these mechanisms would explain why the PRNFLT in the seeing eye of Case 3 was thinner than that of the fellow eye with NLP (Fig. 2). Because the underlying cause for her optic neuropathy has not yet been determined, it is possible that she had other intraocular pathologic conditions that could have contributed to her loss of vision and reduction of PRNFLT. One possibility is that over the 9 years that the patient’s nonseeing eye had been blind, gliosis had occurred, thus thickening the PRNFL compared with the fellow sighted eye which had not yet developed substantial gliosis.

Our findings should be taken into consideration in the interpretation of OCT findings in patients when one is attempting to determine the prognosis for visual recovery in patients with nonglaucomatous optic neuropathies.

REFERENCES

Optic Disc Edema, Cystoid Macular Edema, and Elevated Vascular Endothelial Growth Factor in a Patient With POEMS Syndrome

Deborah Y. Chong, MD, Grant M. Comer, MD, and Jonathan D. Trobe, MD

Abstract: A 48-year-old man with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome had bilateral optic disc edema (ODE), bilateral cystoid macular edema (CME), anasarca, and elevated serum vascular endothelial growth factor (VEGF). This is the first reported example of ophthalmoscopic, angiographic, and optical coherence tomographic evidence of the combination of ODE and CME in this syndrome. This combination of features suggests that the ODE in this condition may be due to increased vascular permeability.

CASE REPORT

A 48-year-old man complained of blurred vision for 3 months and predominantly right eye metamorphopsia for 1 week. He also had increasing abdominal distension and pain, early satiety, shortness of breath, and severe lower extremity pitting edema that elicited a hospital admission.

POEMS syndrome was diagnosed in 1999 on the basis of chronic sensorimotor demyelinating and axonal polyneuropathy, generalized lymphadenopathy, monoclonal gammopathy, and hypogonadism. A sural nerve biopsy had demonstrated axonal loss without evidence of amyloid deposition or vasculitis. Axillary lymph node biopsy had demonstrated angiofollicular lymph node hyperplasia. Later, he developed splenomegaly and hypothyroidism. He did not have diabetes.

The peripheral neuropathy had initially been treated with intravenous immunoglobulin and high-dose intravenous dexamethasone without benefit, but chronic prednisone treatment eventually produced sustained improvement. Mycophenolate mofetil was later added to prednisone, a regimen he continued until the time of his admission.

The ophthalmic history was remarkable only for high myopia and presbyopia.

Best-corrected visual acuity was 20/80 in the right eye and 20/50 in the left eye. Ishihara color plates were normal bilaterally. He described central metamorphopsia in the right eye on Amsler grid testing. A 24-2 Humphrey visual field demonstrated enlargement of the blind spot in the right eye and an inferior nerve fiber bundle defect in the left eye (Fig. 1). Pupils were of normal size and reactivity without a relative afferent pupillary defect. Intraocular pressures were 10 mm Hg in the right eye and 8 mm Hg in the left eye. Ophthalmoscopy revealed bilateral ODE (Fig. 2A) and CME (Fig. 2B). Fluorescein angiography (FA) disclosed bilateral late leakage from the optic discs and late petalloid leakage in the macula consistent with CME (Fig. 2C). The retinal and choroidal vascular perfusions appeared normal. Optical coherence tomography (OCT) revealed bilateral increased macular thickness with perioveal intraretinal hypoechoic cavitations consistent with CME (Fig. 2D). There was no vitreous traction or epiretinal membrane.

Brain and orbit MRI, not shown because of poor resolution owing to patient motion, demonstrated symmetric normal-diameter optic nerves of normal signal intensity...
Optic Disc Edema in POEMS


FIG. 1. 24-2 Humphrey visual fields show enlargement of the blind spot in the right eye and an inferior nerve fiber bundle defect in the left eye.

Pattern deviation

without pathologic contrast enhancement. Optic nerve sheath dilation was present bilaterally. There was no pathologic contrast enhancement, mass, or mass effect within the orbits or the brain. There was no ventriculomegaly, loss of sulcal markings, compromise of cisternal spaces, or periependymal signal changes to suggest elevated intracranial pressure (ICP). Magnetic resonance venography was negative for venous sinus thrombosis. The patient was too ill to undergo a lumbar puncture for relieving pressure.

Serum VEGF and interleukin-6 (IL-6) levels were elevated at 432 pg/mL (normal 31–86 pg/mL) and 10 pg/mL (normal <5 pg/mL), respectively.

The patient was treated with intravenous bevacizumab, an anti-VEGF monoclonal antibody, in combination with oral dexamethasone, and continued mycophenolate mofetil. One month after this regimen was started, the ophthalmic examination was unchanged. In the ensuing 4 weeks, the patient’s systemic condition deteriorated with worsening ascites and shortness of breath. Bevacizumab and dexamethasone were discontinued and replaced with melphalan and prednisone. After 1 month of this therapy, the ophthalmic examination was still unchanged. The patient expired shortly thereafter, and thus repeat serum VEGF and IL-6 levels could not be obtained.

DISCUSSION

The occurrence of ODE in POEMS syndrome, as found in our patient, has been well documented (2–12). The presence of bilateral CME in POEMS syndrome has been reported only once (13). In that case, bilateral CME was present together with late fluorescein staining of the optic discs, but ophthalmoscopic evidence of ODE was not described. We believe our patient to be the first reported example of ophthalmoscopic, angiographic, and OCT evidence of the combination of ODE and CME in this syndrome. We propose that this combination, together with the presence of anasarca and increased serum VEGF, implies that increased vascular permeability is the mechanism of the ODE in POEMS syndrome.

There is a lingering controversy as to whether the ODE of POEMS syndrome is a manifestation of increased ICP, nerve infiltration, ischemia, or vascular hyperpermeability. Some case series (6,8) and case reports (9,10) have documented elevated ICP in patients with POEMS syndrome with bilateral ODE. However, other studies have not found elevated ICP in such patients with bilateral ODE (3,4,7,11,12).

We acknowledge that, given the absence of a lumbar puncture, we were unable to exclude elevated ICP in our patient. We would defend our proposition that the ODE is based on vascular leakage rather than papilledema by citing evidence that CME, defined as petalloid intraretinal fluid-filled cavitations, does not typically occur in papilledema. OCT analysis of 7 patients with papilledema secondary to idiopathic intracranial hypertension or metastatic cancer to the brain and ophthalmoscopic evidence of macular edema showed that the edema was entirely subretinal rather than intraretinal (14).

We also cannot exclude infiltration of the optic nerve by abnormal proteins as the cause of ODE. Case reports have described orbital, choroidal, and/or optic nerve infiltration in POEMS syndrome or Castleman disease, an angiofollicular lymph node hyperplasia that can be associated with POEMS syndrome (15–18). However, we did not observe choroidal lesions on ophthalmoscopy, FA, or OCT. MRI did not show infiltrative lesions in the optic nerves or orbits.

Vascular occlusion and ischemia are also potential causes of ODE. Venous and arterial thromboses have been loosely associated with POEMS syndrome (6). However, the ODE in POEMS syndrome is typically bilateral and would require two separate thrombotic events to occur.

The simultaneous presence of bilateral CME, severe lower extremity edema, and ascites supports the idea that the ODE may result from capillary leakage similar to that happening elsewhere in the body. Elevated serum levels of VEGF, a potent angiogenic and vascular permeability factor, have been documented in POEMS syndrome (7,13,19–21). In 10 patients with POEMS syndrome, Watanabe et al (7) found a mean serum VEGF level of 1,673.2 pg/mL compared with <131 pg/mL in control
subjects. Additionally, serum VEGF levels appear to correlate with disease activity—including the degree of CME—in POEMS syndrome (13,19–21). Macular edema in uveitis, diabetic retinopathy, central retinal vein occlusion, and age-related macular degeneration has been associated with elevated intraocular VEGF levels (22).

With regard to treatment of POEMS syndrome, Badros et al (19) described a patient with serum VEGF levels >2,300 pg/mL who had persistent systemic symptoms after treatment with melphalan and dexamethasone, but who had a dramatic improvement in edema and peripheral neuropathy after intravenous bevacizumab was
added to the regimen. Further investigation is needed to determine whether anti-VEGF agents, alone or in conjunction with other agents, may ameliorate the symptoms of POEMS syndrome. If anti-VEGF agents can resolve the ODE in POEMS syndrome, that will lend further support to the hypothesis that the ODE in this syndrome results from increased vascular permeability.

REFERENCES

Choroidal and Optic Nerve Infarction in Hepatitis C-Associated Polyarteritis Nodosa

Yanina Kostina-O’Neil, MD, Guy V. Jirawuthiworavong, MD, MA, David N. Podell, MD, PhD, and Robert L. Lesser, MD

Abstract: A 39-year-old man presented with headache, weight loss, bilateral subdural hematomas, pansinusitis, and visual loss. The neuro-ophthalmologic examination disclosed deep choroidal lesions and bilateral optic disc edema. Orchietomy for testicular torsion showed acute vasculitis consistent with polyarteritis nodosa (PAN). Polymerase chain reaction (PCR) testing revealed hepatitis C. This is the first reported case of PAN due to hepatitis C with early findings of choroidal and optic nerve infarction.

CASE REPORT

A 39-year-old Caucasian man developed severe headache, difficulty reading, photophobia, and unsteady gait. Over the past 6 months, he had had nasal congestion and an unexplained 20–30 pound weight loss with night sweats. He was a heavy smoker, denied intravenous drug use, and had multiple sex partners and tattoos. There was no history of connective tissue disease.

White blood count was $27.9 \times 10^3 \mu L$, hemoglobin was 12.2 g/dL, hematocrit was 42.5%, platelet count was $509 \times 10^3 \mu L$, and the creatinine level was 0.6 mg/dL. Results of an electrocardiogram (ECG) were normal. Neurologic examination showed ataxia and impairment of fine movements of the right hand. Brain MRI showed pansinusitis and bilateral subdural hematomas with a 4 mm midline shift (Fig. 1). Brain MRA was negative.

The left subdural hematoma was evacuated. Postoperatively, the brain CT scan showed a decrease in the size of the left subdural hematoma. Shortly thereafter, he reported a 1-month history of epistaxis, pain in the right periorcular region and base of the skull, and a decline in vision such that he could barely read the headline of a newspaper. Results for repeat brain MRI were unchanged.

Three weeks later, a neuro-ophthalmologic examination disclosed best-corrected visual acuities of 20/60 in the right eye and 20/20 in the left eye. Pupils were normal in size and reactivity without an afferent pupillary defect. There was mild injection of the conjunctiva bilaterally and 1+ cell in the anterior chamber of the right eye. Intraocular pressures were normal. Automated perimetry revealed visual field defects most marked temporally and greater in the right eye than in the left eye (Fig. 2).
Polyarteritis Nodosa

Ophthalmoscopy revealed bilateral optic disc edema with flame-shaped hemorrhages. Multiple deep, well-circumscribed, white choroidal lesions were present in the posterior poles of both eyes (Fig. 3). Fluorescein angiography showed optic disc leakage and well-circumscribed choroidal areas of late staining. Brain MRI with venography (MRV), performed because the optic disc might have signaled increased intracranial pressure, showed no sign of dural sinus thrombosis.

The patient was treated with clarithromycin for pansinusitis. A further workup revealed the following: alanine aminotransferase (ALT), 229 U/L; aspartate aminotransferase (AST), 136 U/L; alkaline phosphatase, 241 U/L; albumin, 3.0 g/dL; erythrocyte sedimentation rate (ESR), 85 mm/h; RF, 90 (normal 0-39); positive urine protein; and normal titers for HIV, cytomegalovirus (CMV), toxoplasmosis, and histoplasmosis. Results of tests for Lyme disease, antiphospholipid antibodies, perinuclear (P)-antineutrophilic cytoplasmic antibodies (ANCAs) (<1:40) and cytoplasmic (C)-ANCAs (<1:40), purified protein derivative (PPD), reactive plasma protein (RPR), fluorescent treponema antibodies-absorbed (FTA-ABS), aspergillus antigen, and complement 3 (C3), and complement 4 (C4) were also normal or negative as were a chest x-ray and blood cultures.

The patient was scheduled for a sinus biopsy, but 2 days before the biopsy, he developed severe groin pain. A urologist diagnosed testicular torsion and acute epididymitis. After emergency unilateral orchiectomy, pathologic
FIG. 4. Histopathology of the testis and epididymis. A. Low magnification shows acute vasculitis with fibrinoid necrosis of small- and medium-sized arteries (arrow) consistent with PAN. B. Similar findings are demonstrated under high magnification. No granulomatous features were identified.

Ten days later, visual acuity decreased to 20/300 in the right eye and to 20/40 in the left eye. Ophthalmologic examination disclosed diffuse bilateral scleritis and anterior nongranulomatous uveitis in the right eye. The choroidal lesions were larger and coalescing (Fig. 5).

Treatment was begun immediately with 1 g intravenous methylprednisolone for 1 day followed by 60 mg prednisone/day and 81 mg aspirin/day. Two days later, the patient developed mild substernal and left axillary chest pain. An ECG showed a myocardial infarction; cardiac catheterization showed occlusion of the left circumflex artery. The posterior descending artery and left ascending artery had imaging changes consistent with vasculitis. The patient was treated with 60 mg prednisone daily, 50 mg cyclophosphamide 3 times per day, 3 million units alfa-2b interferon 3 times per week subcutaneously, and 600 mg ribavirin twice per day. Subsequently, a polymerase chain reaction (PCR) test confirmed that the patient was hepatitis C-positive with a viral load of >1 million copies. Results of cryoglobulin testing were negative.

Hepatitis C-related systemic necrotizing vasculitis consistent with PAN was diagnosed. The result of a repeat P-ANCA measurement was 1:80 (negative <1:40). The scleritis and iritis improved. Three weeks after initiation of therapy, the choroidal lesions significantly diminished in size and eventually disappeared. Visual acuity improved to 20/50 in the right eye and 20/20 in the left eye. Three months after systemic treatment, ophthalmoscopy disclosed subretinal fibrosis, atrophy of the retinal pigment epithelium (RPE), and temporal pallor of the optic disc in the right eye. In the left eye, there was atrophy of the RPE and optic disc pallor (Fig. 6). Six months after treatment, he developed a juxtafoveal choroidal neovascular membrane in the right eye that was treated with a photodynamic laser.

After 12 months of therapy, cyclophosphamide was discontinued, and the patient remained in remission with visual acuities of 20/100 in the right eye and 20/20 in the left eye.

Seven years after the initial illness, visual acuity in the right eye dropped to finger counting due to further RPE atrophy. The visual field in the right eye showed residual paracentral and cecocentral field loss; the visual field in the left eye showed minimal paracentral depression (Fig. 7).

DISCUSSION

Our patient presented with prominent choroidopathy and optic neuropathy as early signs of hepatitis C-associated PAN. These features are similar to those reported by Hsu et al (7), who described a 70-year-old woman with PAN.
unassociated with hepatitis C who presented with a central retinal artery occlusion in the right eye and anterior ischemic optic neuropathy with choroidal infarction in the left eye. The single area of choroidal infarction was triangular in shape and was referred to as “the triangular sign of Amalric.” In contrast to the case of Hsu et al (7), the choroidal lesions in our patient were round, bilateral, distinct, multiple, and small, similar to those in acute multifocal placoid pigment epitheliopathy (AMPPE). In our patient, the lesions resolved in about 4 weeks, leaving areas of RPE atrophy. The ophthalmic findings in our patient do indeed resemble those of AMPPE, a self-limited condition that presents with multiple yellow-white placoid subretinal lesions in the posterior pole and usually has a good prognosis with relatively fast recovery with or without systemic therapy (8). Hsu et al (9) reported a patient who presented with AMPPE and had vasculitis with features of Wegener granulomatosis and atypical PAN. Pinto Ferreira et al (10) reported a patient with PAN whose lesions resembled AMPPE in one eye and serpiginous choroidopathy in the other eye. AMPPE has been reported with cerebral vasculitis (11) and meningoencephalitis (12). Although Gass (8) proposed that the disease process was at the level of the RPE, recent imaging and pathology reports have shown that the underlying problem is in the choroid (13).

Newman et al (14) reported a case of recurrent monocular peripheral visual field constriction sparing acuity in a patient with PAN. Pathologic examination of the orbital and ocular vessels at autopsy showed vasculitis of the short posterior ciliary and small- and medium-sized orbital arteries but not the ophthalmic and central retinal arteries. The authors attributed the episodes of transient peripheral visual loss to intermittent choroidal vascular ischemia.

Our patient is also unusual in having hepatitis C. Chronic hepatitis C virus (HCV) infection is associated with small vessel vasculitis [mixed cryoglobulinemia (MC)] or medium-size vessel vasculitis (PAN). Anti-HCV antibodies are found in 60%-80% of patients with MC but only in 5%-12% of patients with PAN (15). Other extrahepatic systemic manifestations of hepatitis C include palpable purpura, porphyria cutanea tarda, Mooren corneal ulcer, sicca syndrome, uveitis, B-cell lymphoma, and glomerulonephritis (16).

The diagnosis of hepatitis C is made by testing for anti-HCV using an enzyme immunoassay (EIA). Testing for HCV RNA using a sensitive assay such as PCR or transcription-mediated amplification (TMA) is the most effective method to confirm HCV infection. Although results of liver function tests can be normal, the presence of
HCV-RNA in serum indicates active infection (15,17). Risk factors for hepatitis C include intravenous drug use and blood transfusions received before 1987. Hepatitis C is treated with pegylated interferon in combination with ribavirin.

For untreated PAN, the aggregate 1-year survival rate is 50%, and the 5-year survival rate is 13% (18–21). Major causes of death include mesenteric, renal, cardiac, or cerebral infarction (3). Complications may occur in clinically inactive disease when scarring of inflamed vessels causes narrowing of the vascular lumen.

Treatment for PAN includes corticosteroids and immunosuppressive agents such as cyclophosphamide and azathioprine. Although the 5-year survival rate improves to 50% with corticosteroid treatment alone, it is as high as 80% with a combination regimen that consists of corticosteroid and cyclophosphamide. (22) If treatment is started early, preservation of tissue function is more likely (1–3), hence the need for early recognition of the connection between PAN and the ophthalmic signs demonstrated in our patient.

REFERENCES

Primary Sinonasal Undifferentiated Carcinoma Presenting With Bilateral Retrobulbar Optic Neuropathy

Madhura A. Tamhankar, MD, Nicholas J. Volpe, MD, Laurie A. Loevner, MD, James N. Palmer, MD, and Michael Feldman, MD, PhD

Abstract: A 43-year-old man presented with acute bilateral visual loss. Ophthalmologic examination revealed no light perception in the right eye and a visual acuity of 20/50 in the left eye with a right afferent pupillary defect. Ophthalmoscopic examination was normal. Brain MRI showed an intracranial but extra-axial mass in the floor of the anterior cranial fossa extending along the olfactory groove and into the sinonasal vault. Endoscopic biopsy showed a high-grade neoplasm consistent with sinonasal undifferentiated carcinoma. This case report highlights an unusual clinical presentation for this rare and aggressive neoplasm.

S


(Sinonasal undifferentiated carcinoma (SNUC) is a rare aggressive neoplasm of the nasal cavity and paranasal sinuses (1). Presenting signs and symptoms typically include nasal obstruction, epistaxis, rhinorrhea, proptosis, and facial pain. Although visual loss from orbital invasion can occur, acute visual loss due to direct compression of intracranial visual pathways without orbital invasion is highly unusual. We report such an occurrence for the first time.

CASE REPORT

A previously healthy 43-year-old man presented with acute loss of vision in the right eye noted upon awakening. The patient denied any associated symptoms such as pain with eye movement, transient visual obscurations, or diplopia. There was no history of epistaxis, nasal obstruction, facial pain, or rhinorrhea. He did report mild headaches in the frontal region 2 weeks before presentation. Past medical history included a right facial palsy due to Lyme disease 8 months before presentation with complete recovery after a course of intravenous antibiotics.

Ophthalmologic examination revealed no light perception in the right eye and a visual acuity of 20/50 in the left eye. There was a right afferent pupillary defect. Results of intraocular pressures, ocular motility, and the anterior segment examination were normal in both eyes. Ophthalmoscopic examination revealed normal-appearing optic nerves bilaterally without evidence of swelling or pallor. Visual field testing showed a dense inferior visual field defect in the left eye that also involved the superior and temporal quadrants. Results of the patient's neurologic and general examinations were within normal limits.

Brain MRI revealed an intracranial extra-axial mass lesion along the floor of the anterior cranial fossa extending along the olfactory groove and involving the sinonasal vault (Fig. 1). Dural enhancement was noted along the undersurface of the frontal lobes bilaterally and along the falk cerebri in the anterior interhemispheric fissure. The mass extended posteriorly along the planum sphenoidale into the tuberculum sella and around the right anterior clinoid process. Enhancement was also present around both the prechiasmatic optic nerves. Diagnostic considerations included a dural-based malignancy such as a meningioma, lymphoma, esthesioneuroblastoma, or metastatic tumor.

The patient was treated with intravenous dexamethasone. Over the next 24 hours, vision in the left eye continued to decline to 20/200. Accordingly, the patient underwent endoscopic surgical biopsy of the mass in the sinonasal vault. An ill-defined mass was identified along the roof of the right ethmoid. It extended through the cribriform plate and into the adjacent dura and the olfactory bulb. Biopsies were obtained from the roof of the right ethmoid cavity and anterior skull base as well as from the left ethmoid sinus. A frozen section was consistent with carcinoma. A free temporalis fascia graft was placed over the medial ethmoid roof and skull base for reconstruction and prevention of a cerebrospinal fluid leak. The lesion was considered unresectable because of extensive intracranial spread and involvement of prechiasmatic optic nerves.

Pathologic examination (Fig. 2) showed irregular sheets and nests of small- to intermediate-sized tumor cells, with high nuclear/cytoplasmic ratios, hyperchromatic nuclei, absence of nucleoli, and extensive mitoses. There was nuclear molding and a focal crush artifact. Squamous or glandular differentiation, fibrillary stroma, ganglion cells, calcifications, or rosettes were not identified. The initial morphologic impression suggested a small cell neuroendocrine carcinoma. Immunostains showed that the tumor cells were positive for low molecular weight cytokeratin CAM 5.2 and pan-cytokeratin. However, the tumor cells were negative for synaptophysin, chromogranin, and neurofilament protein, arguing against a neuroendocrine carcinoma. The morphologic and immunophenotypic features were consistent with SNUC. Additional characterization was not possible because of lack of sufficient tissue.

Results of a metastatic workup including a bone scan and bone marrow biopsy were negative. The patient underwent palliative treatment with whole-brain irradiation (5,600 cGy in 26 fractions over 40 days) and chemotherapy with cisplatin and etoposide. He died of spinal metastasis 18 months after presentation.

DISCUSSION

An interesting feature of the current case is that, despite the extensive spread of tumor, our patient denied any sinonasal symptoms. A more unusual finding is that the sudden onset of visual loss was due to bilateral retrobulbar optic nerve involvement by the tumor without orbital extension. Compressive lesions that involve the anterior visual pathway usually cause a gradual and insidious loss of visual function (2,3). In rare instances, mass lesions may produce a sudden onset of visual loss that clinically presents as an acute optic neuritis. This occurrence has been reported in patients with pituitary adenoma, craniopharyngioma, mucoceles, and pyoceles of the paranasal sinuses and in sphenoid sinus esthesioneuroblastoma (4-7) but not in SNUC.
Several mechanisms have been proposed to explain the sudden visual loss that occurs with intracranial mass lesions. These can include hemorrhage and ischemia due to vascular compression of the visual pathways. Demyelination and axonal degeneration of the prechiasmatic optic nerves due to compression by tumors have been shown in histopathologic studies (4,5). Clinical features of inflammatory optic neuropathy, including corticosteroid responsiveness, have been associated with some compressive lesions such as medulloblastoma, plasmacytoma, and pituitary adenoma. (6–9).

SNUC was first described in 1986 as a rare and highly aggressive neoplasm arising from the nasal cavity and paranasal sinuses (1). These tumors tend to be large and expansile, with widespread involvement of the nasal cavity and paranasal sinuses. Bone destruction and invasion of adjacent structures such as the orbit, cranial vault, and skull base is frequently seen (10–12). The vast majority of affected patients present with epistaxis, rhinorrhea, nasal obstruction, and facial pain (1,12–14). However, some patients, like our patient, have surprisingly few subjective symptoms despite extensive disease at presentation (13,15).

The differential diagnosis of SNUC includes lymphoepithelioma-like carcinoma, small cell neuroendocrine carcinoma, esthesioneuroblastoma, lymphoma, melanoma, and rhabdomyosarcoma, among others. Although detailed histopathologic differential diagnosis is beyond the scope of this report, the morphologic and available immunophenotypic features of the current neoplasm fit best with a diagnosis of SNUC.

Overall survival of patients with SNUC is poor in most reported series (1,10,12,15–17). Treatment modalities have been varied and involve radiotherapy, chemotherapy, and surgery (1,10,12,13,15–21). Control of local disease is the main therapeutic consideration. Although no clear consensus exists regarding treatment, a multidisciplinary approach combining surgery (craniofacial resection) with chemotherapy and radiation may be used to control local disease (1,10,14). The extent of disease at diagnosis represents the most sensitive predictor for survival.

REFERENCES


Terson Syndrome With Bilateral Optic Nerve Sheath Hemorrhage

Chiaki D. Gauntt, MD, PhD, Richard G. Sherry, MD, and Chithra Kannan, MD

Abstract: A 53-year-old man presented with an acute headache and mental status changes due to rupture of an anterior choroidal artery aneurysm. A preoperative CT scan demonstrated subarachnoid hemorrhage, bilateral optic nerve sheath hemorrhage, and bilateral intraocular hemorrhage. Ophthalmoscopy and B-scan ocular ultrasound disclosed vitreous hemorrhages, features consistent with Terson syndrome. This is the first CT report of Terson syndrome showing bilateral optic nerve sheath hemorrhage.


A 53-year-old Vietnamese man had the acute onset of severe headache, weakness, and depressed consciousness and was admitted to the hospital. He had no significant past medical or ocular problems and was not taking any medication.

The preoperative CT scan (Fig. 1) clearly depicted extensive subarachnoid hemorrhage in the basal cisterns and in the intraorbital optic nerve segments. Hemorrhage was also conspicuous in the posterior globes adjacent to the optic discs. Its proximity to the optic discs suggested that it was subhyaloid. Lumbar puncture confirmed a subarachnoid hemorrhage. Cerebral angiography demonstrated an aneurysm arising from the origin of the right anterior choroidal artery. The patient underwent emergency external ventriculostomy and later endovascular coil treatment of the aneurysm.

One week after admission, the patient’s general condition stabilized, and the first complete eye examination
was performed. Vision was not assessed because the patient was stuporous. Pupils were 3 mm and equal, responding to light stimulation without a relative afferent pupillary defect. Anterior segment examination showed no abnormalities and intraocular pressures were normal. Dilated fundus examination revealed extensive vitreous hemorrhage in both eyes with no view of either retina. B-scan ultrasonography of the eyes demonstrated findings consistent with large amounts of intraocular hemorrhage dispersed in the vitreous cavity bilaterally (Fig. 2).

The patient received physical therapy and was transferred to a rehabilitation facility, with a plan of possible future vitrectomy.

This patient had Terson syndrome, intraocular hemorrhage due to acutely elevated intracranial pressure usually associated with subarachnoid hemorrhage or severe head trauma (1-7). To our knowledge, neuroimaging of an intrasheath hemorrhage in Terson syndrome has not been previously reported.

The mechanism of Terson syndrome has been extensively debated (8-12). The earliest speculation was that intracranial blood extends directly into the intraocular space. Some investigators believe that the increased intracranial pressure is transmitted to the retinal veins, causing their rupture (8,9). Other authors (11,12) propose a mechanism in which a sudden rise in intracranial pressure is transmitted through the optic nerve sheath to the optic nerve head, causing rupture of the peripapillary capillaries.

Clinically the intraocular hemorrhage may be seen as subretinal, retinal, preretinal or subhyaloid, or intravitreal. Subhyaloid hemorrhage may disperse into the vitreous cavity as seen in our patient. The intraocular hemorrhage spontaneously resolves in several months in most patients. Vitrectomy is occasionally needed in patients with non-resolving vitreous hemorrhage.

REFERENCES

Intrinsically Photosensitive Retinal Ganglion Cells

Aki Kawasaki, MD and Randy H. Kardon, MD, PhD

Abstract: The recent discovery of melanopsin-expressing retinal ganglion cells that mediate the pupil light reflex has provided new insights into how the pupil responds to different properties of light. These ganglion cells are unique in their ability to transduce light into electrical energy. There are parallels between the electrophysiologic behavior of these cells in primates and the clinical pupil response to chromatic stimuli. Under photopic conditions, a red light stimulus produces a pupil constriction mediated predominantly by cone input via transsynaptic activation of melanopsin-expressing retinal ganglion cells, whereas a blue light stimulus at high intensity produces a steady-state pupil constriction mediated primarily by direct intrinsic photoactivation of the melanopsin-expressing ganglion cells. Preliminary data in humans suggest that under photopic conditions, cones primarily drive the transient phase of the pupil light reflex, whereas intrinsic activation of the melanopsin-expressing ganglion cells contributes heavily to sustained pupil constriction. The use of chromatic light stimuli to elicit transient and sustained pupil light reflexes may become a clinical pupil test that allows differentiation between disorders affecting photoreceptors and those affecting retinal ganglion cells.

The discovery of melanopsin and a subset of intrinsically photosensitive retinal ganglion cells containing this photopigment has provided an anatomic basis for explaining these clinical puzzles and has prompted a new look at the connections between the retina and the brain.

In addition to their role in circadian entrainment, the melanopsin-expressing retinal ganglion cells mediate the pupillary light reflex. Axonal projections of the melanopsin-expressing cells to the midbrain represent the major retinal input to the olivary pretectal nucleus of the midbrain (14, 15). Although there is evidence from a primate model that melanopsin-expressing ganglion cells may contribute to conscious visual perception, they do not appear to have the functional properties for direct image formation (16).

Here we review some of the anatomic and physiologic aspects of the melanopsin-expressing ganglion cells and emphasize the relationship between the functional properties of the melanopsin-expressing ganglion cell in primates and the pupil light reflex in health and disease states of the retina and optic nerve.

**BIOLOGIC ROLE OF MELANOPSIN-EXPRESSING RETINAL GANGLION CELLS**

The mammalian eye has two different sensory systems that respond to different qualities of light. The classic photoreceptor system (rods and cones) serves the familiar function of image formation which, by way of connections and processing by recipient neurons in the retina and visual cortex, provides for conscious visual perception. In contrast, the newly recognized melanopsin photoreceptive system functions in irradiance detection, much like a direct-current (DC) light meter. Irradiance detection is a measure of environmental brightness and occurs at a subconscious level. Irradiance detection serves...
to align biologic rhythms to the solar day, that is, setting the circadian clock.

The master circadian pacemaker in mammals is the suprachiasmatic nucleus (SCN) in the anterior hypothalamus. A direct monosynaptic neuron pathway linking the eye to the SCN, called the retinohypothalamic tract, has been known for decades (Fig. 2) (19,20). Recent investigations have demonstrated that the melanopsin-expressing ganglion cells innervate the SCN and form the retinohypothalamic tract (3,4,21). These ganglion cells also project to other central sites that modulate the SCN and regulate the circadian clock, including the intergeniculate division of the lateral geniculate nucleus, the ventral subparaventricular zone of the hypothalamus, and the ventrolateral preoptic nucleus (22).

The melanopsin-expressing retinal ganglion cells also project to the olivary pretectal nucleus (OPN) of the dorsal midbrain, forming the afferent limb of the pupillary light reflex (4). This direct connection to the main pupil integrating center by intrinsically photosensitive cells explains why persons blind from photoreceptor disease can still have an intact pupil light reflex and appropriate day-night cycles and may provide a clue for the basis of their photosensitivity. Other non-image-forming functions mediated by the melanopsin-expressing retinal ganglion cells are melatonin secretion by the pineal gland, light-induced suppression of locomotor activity in rodents (termed negative masking), and circadian-independent regulation of sleep and heart rate (22).

Although the biologic functions of the classic and melanopsin photoreceptive pathways are widely different, there is also evidence of some interaction between them (7,22). Perhaps the most convincing finding comes from intracellular recordings showing that activation of short-wavelength cones attenuates the responses of the melanopsin-expressing retinal ganglion cells, whereas activation of medium-wavelength and long-wavelength cones and rods excites the melanopsin-expressing retinal ganglion cells (16). Additionally, retrograde tracer studies do not rule out the possibility that sites participating in image formation, such as the dorsal lateral geniculate nucleus, may receive

**FIG. 2.** Schematic summary of brain regions and circuits influenced by melanopsin-expressing retinal ganglion cells. The melanopsin-expressing retinal ganglion cells and their axons are shown in dark blue and their principal targets in red. Projections of these ganglion cells to the suprachiasmatic nucleus (SCN) form the bulk of the retinohypothalamic tract and contribute to photic entrainment of the circadian clock. The orange pathway with green nuclei shows a polysynaptic circuit that originates in the SCN and photically regulates melatonin release by the pineal gland (P) through its sympathetic innervation. Synaptic links in this pathway include the paraventricular nucleus (PVN) of the hypothalamus, the intermediolateral nucleus (IML) of the spinal cord, and the superior cervical ganglion (SCG). Another direct target of melanopsin-expressing retinal ganglion cells is the olivary pretectal nucleus (OPN), a crucial link in the circuit underlying the pupillary light reflex, shown in light blue (fibers) and purple (nuclei). Synapses in this parasympathetic circuit are found at the Edinger-Westphal nucleus (EW), the ciliary ganglion (CG), and the iris muscles (I). Other central targets include two components of the lateral geniculate nucleus of the thalamus, the ventral division (LGNv), and the intergeniculate leaflet (IGL). (Reprinted with permission from reference 9.)
some melanopsin projections. Taken together, these findings suggest that irradiance detection may have a modulating influence on conscious visual perception (16,22).

ANATOMICAL AND FUNCTIONAL FEATURES OF MELANOPSIN-EXPRESSING RETINAL GANGLION CELLS

Melanopsin-expressing retinal ganglion cells represent a fractional subset of the total ganglion cell population of the eye: approximately 0.3% in primates (16). These ganglion cells are morphologically distinguished by their giant-sized soma and extremely large dendritic field size (Fig. 3). The long, sparsely branching dendritic processes extend into the inner and outer sublayers of the inner plexiform layer where they interconnect and form a bilayered anatomic syncytium that spirals around the foveal pit. This bilayered dendritic meshwork, called a “photoreceptive net,” represents a distinctive anatomic model that appears suited to a “broad-capture” integration of light over long periods of time. Contrast this model to the “narrow-capture” photoreceptive model of rods and cones, which is specialized for encoding fine spatial resolution and a transient, adaptable response (23).

Although the biochemical molecular cascade mediating melanopsin-based phototransduction is not yet fully elucidated, light activation of this pathway results in direct depolarization of the ganglion cell with generation of fast action potentials. The intrinsic photoactivation of melanopsin-expressing retinal ganglion cells has a relatively higher

FIG. 3. Morphology of melanopsin-immunoreactive cells. A. Human cell (arrow); propidium iodide red counterstain. Scale bar, 50 mm. B. Macaque cell (arrow). Scale bar, 50 mm. C. Macaque retina tracing; dots represent melanopsin-expressing cells. T, temporal retina; N, nasal retina; S, superior retina; I, inferior retina. D. Melanopsin-expressing ganglion cells in peripheral retina (left; scale bar, 100 mm). Tracing of a peripheral horseradish peroxidase (HRP)-stained giant cell (right; scale bar, 200 mm). Parasol and midget cells (far right) are shown for comparison. E. Melanopsin-expressing cells encircling the fovea (left; scale bar, 100 mm). Tracings of two HRP-stained giant cells, 1–1.5 mm from the fovea (right; scale bar, 200 mm). Circles (far right) indicate size of foveal parasol and midget cells. F. Dendritic field size of melanopsin cells versus eccentricity (inner cells, filled circles, n = 93; outer cells, open circles, n = 63). Parasol (filled diamonds, n = 333) and midget cells (open diamonds, n = 93) are shown for comparison. G. Mean cell density of melanopsin cells versus eccentricity (total 614 cells in 78 1 mm² samples). H. Dendritic arbors (green) of melanopsin cells (arrows) from stacked confocal images of 5 consecutive vertical sections (25 mm thick). The soma of the outer cell is displaced to the inner nuclear layer (INL). Scale bar, 50 mm. GCL, ganglion cell layer; IPL, inner plexiform layer. (Reprinted with permission from reference 16.)
threshold to light compared with rod-mediated and cone-mediated light responses. In addition, the intrinsic activation has a longer latency time and a characteristic pattern of discharge of action potentials. The discharge rate builds relatively slowly and reaches a maximal firing rate that is maintained linearly proportional to light intensity (Fig. 1, inset) (8,9,16). If a bright light is left on, the cell firing rate is remarkably steady and sustained without evidence of fatigue or adaptation to the continuous light stimulation. When the light is turned off, the cell does not immediately stop firing but gradually decreases its firing rate until it ceases. This may occur 10–15 seconds or more after the light stimulus has been removed, depending on the brightness of the light. In classical phototransduction, the rods and cones hyperpolarize in response to light activation, have very short latency times to onset of ganglion cell firing, and demonstrate early adaptation. The features of the classical photoreceptors are compared with those of the ganglion cell photoreceptors in Table 1.

Another characteristic feature of the intrinsic phototransduction pathway of the melanopsin-expressing ganglion cells is a broad spectral sensitivity with a peak in the short-wavelength range (blue light toward 484 nm in rats and 482 nm in macaque monkeys) (9,16). Why is there sensitivity to blue light? One investigator (24) has speculated that it has to do with setting the circadian clock, noting that 480 nm light is the dominant wavelength at dawn and at dusk.

Despite the various anatomic and physiologic differences between these two types of photoreceptors, they are functionally complementary and synergistic systems for driving the pupil light reflex. Hattar et al (25) conclusively demonstrated this interaction in mice using three genetically modified strains. Melanopsin-knockout mice (melanopsin gene ablated, but this class of retinal ganglion cell is still present and functioning) showed a recordable but incomplete pupil response to bright light, proving that rods and cones alone can drive the pupil light reflex but only to a certain extent. On the other hand, rodless and coneless mice were capable of generating a maximal pupil constriction to bright light in the action spectrum of melanopsin but with greatly reduced sensitivity. Finally, melanopsin-knockout mice also lacking rod and cone function failed to show any pupil light reflex regardless of the brightness or wavelength of the stimulus (25). Recently, S. Hattar et al (personal communication, March 2007) showed that genetic ablation of melanopsin-containing retinal ganglion cells severely attenuates light-dependent physiologic functions, including the pupil light reflex, giving further evidence that this class of intrinsically photosensitive retinal ganglion cells mediates most of the afferent portion of the pupil light reflex.

Although we assume that a dual photoreceptor system also exists in higher animals and humans, confirmation still awaits a systematic study of the pupil light reflex in patients with known gene mutations affecting phototransduction.

**ELECTROPHYSIOLOGY OF MELANOPSIN-EXPRESSING GANGLION CELLS IN PRIMATES**

Electrophysiologic studies have provided some details on the functional properties of melanopsin-expressing retinal ganglion cells in primates. Dacey et al (16) recorded the firing activity of individual melanopsin-expressing ganglion cells isolated from intact in vitro retina of macaque monkeys. After pharmacologic blockade of rod and cone function, they found that the ganglion cell activity

<table>
<thead>
<tr>
<th>TABLE 1. Features of the classic (visual) photoreceptive pathway and the melanopsin (nonvisual) photoreceptive pathway in the mammalian eye</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Photoreceptor cell</strong></td>
</tr>
<tr>
<td>Location</td>
</tr>
<tr>
<td>Photopigment</td>
</tr>
<tr>
<td>Total number</td>
</tr>
<tr>
<td>Receptive field</td>
</tr>
<tr>
<td>Properties</td>
</tr>
<tr>
<td>λ sensitivity</td>
</tr>
<tr>
<td>Function</td>
</tr>
</tbody>
</table>
mediated solely by its intrinsic activation (the melanopsin pathway) was characterized by a long latency time before the first spike, slow build-up to the maximum firing rate, and maintenance of a tonic firing rate proportional to light intensity for the duration of the light stimulus. After light termination, the firing rate did not abruptly cease but rather exhibited a slow, gradual diminution to eventual cessation, features previously noted in rodent ganglion cells (7,9).

Dacey et al (16) also studied the spectral sensitivity of the melanopsin-expressing retinal ganglion cells and their firing behavior as a function of light intensity (Fig. 4). To a low intensity 610 nm (red) light of 10 seconds' duration, they noted a rapid-onset, maximal burst of cell firing that attenuated and ceased (adapted) during the light stimulus, that is, a transient cell response. At higher intensity (by approximately 3 log units), cell firing was present for the duration of the light stimulus, but it demonstrated considerable attenuation. When the light was turned off, there was a correspondingly rapid OFF response of cell activity. This pattern of cell firing to a red light stimulus is consistent with a cone-driven, transient, adapting response. A low intensity, blue light stimulus (470 nm) evoked a rapid-onset cell firing rate that attenuated over the duration of the light stimulus. However, when the same blue stimulus was given at a 3 log unit brighter intensity, the cell maintained a steady rate of firing that persisted for more than 10 seconds after the light was turned off. This pattern of cell firing to bright blue light is consistent with a summed input from cone activation and intrinsic activation. The authors proposed that the melanopsin-mediated response may serve to compensate for the attenuation, or transience, of cone input to deliver steady-state light information to the brain (16).

Is there a clinical corollary to the electrophysiologic behavior of the melanopsin-expressing ganglion cell? Because these cells convey the primary light input to the olivary pretectal nucleus of the midbrain, the pupil light reflex might be expected to reflect the observed activity of the melanopsin-expressing retinal ganglion cells. This is supported by a recently published study by Gamlin et al (15), who confirmed loss of the photoreceptor-mediated transient pupil light reflex to red light but not to bright blue light after pharmacologic photoreceptor blockade in the monkey using intravitreal injections.

THE PUPILLARY LIGHT REFLEX REVISITED

Most clinical studies of the pupil light reflex have emphasized its transient response properties including the
briskness, latency, and amplitude of pupil constriction to a brief, bright white light stimulus (26–30). Other studies have also assessed the pupil response to longer duration light stimuli including both steady-state pupil size and “pupil escape,” in which the pupil dilates or “gives way” during adaptation to continuous light (31,32).

Figure 5 depicts a typical pupil response to a 10 second bright light in a normal human subject. Note that there are two components forming the response waveform during the constriction phase. When the light stimulus is turned ON, there is a rapid-onset, high-velocity pupil constriction until it reaches a minimum pupil size (maximal constriction amplitude). This early transient response is quickly followed by pupillary redilation, or escape, to a more sustained state of partial pupil constriction that continues for the remainder of the light stimulus. Later, we will provide some preliminary evidence that the transient and sustained components of the pupil light reflex in humans can be explained by the proportional light input from the rod and cone photoreceptors and intrinsic retinal ganglion cell photoactivation.

Until recently, the transient and sustained behavior of the pupil to light onset did not have a solid electrophysiologic foundation on which to understand its response to light varying in intensity, duration, and color. The electrophysiologic behavior of the melanopsin-expressing retinal ganglion cells provides a much-needed framework for understanding the pupil light reflex in healthy and disease states to varying conditions of light stimulus. This framework provides a basis for optimal use of the pupil light reflex in clinical practice and confers new significance to the use of the transient and sustained pupil response for diagnosis and differentiation of diseases of the optic nerve and photoreceptors.

Pupil responses mediated by intrinsic activation of the melanopsin-expressing retinal ganglion cells in primates have recently been isolated using pharmacologic blockade of the rod and cone input (15). The recorded pupil responses matched the electrophysiologic behavior of the melanopsin-expressing ganglion cells in terms of chromatic sensitivity, intensity-dependent response, and response pattern to light onset and termination. In a normal monkey eye stimulated with equiluminant red and blue light, rapid-onset pupil constriction was elicited from both stimuli, but the maximum constriction amplitude was greater and more sustained with blue light under constant illumination. This action is presumably due to intrinsic ganglion cell activation superimposed on cone activation. Furthermore,

![Diagram of pupil response](image-url)

**FIG. 5.** Example of a pupillographic recording to a 5 second bright white light in a normal human subject. There are two components forming the response waveform during the constriction phase. When the light is turned ON, the transient phase is characterized by a short-latency, high-velocity maximal change in pupil size. Thereafter, the pupil partly redilates, or escapes, to a state of partial pupil constriction that represents the sustained phase of the pupil light reflex.
FIG. 6. Example of pupillographic recordings to equiluminant chromatic light stimuli in a normal human subject. The pupil responses shown in red were elicited using a long-wavelength (600–620 nm bandwidth) red light of long duration (60 seconds) at 3 different light intensities (1, 10, and 100 cd/m²). The pupil responses shown in blue were elicited using a short-wavelength (465–485 nm bandwidth) blue light of similar duration and intensities. The y-axis shows the pupil size in relative units of pupil diameter (not in mm units). The blue light stimulation produces a larger pupil constriction amplitude compared with red light stimulation at all intensities, presumably due to intrinsic activation of the melanopsin photoreceptive pathway that is additive to the cone activation when a blue light is used. Also note that the sustained pupil response to blue light shows no adaptation, particularly at higher intensities (10 and 100 cd/m²), during 60 seconds of continuous light stimulation compared with the sustained pupil response to red light, which does show adaptation (pupil escape after an initial transient constriction).

The constricted state of the pupil persisted after removal of the light stimulus only when the short wavelength (blue) light stimulus was used. After the monkey eye was treated with an intravitreal injection to pharmacologically inhibit all rod and cone phototransduction, no pupil response could be elicited by red light over a large range of light intensities. However, a bright blue light elicited a delayed, slow, and persistent pupil constriction having a distinct waveform in these primates, which are devoid of functioning rods and cones. In normal humans, Gamlin et al (15) also demonstrated a differential pupil response to red and blue light that paralleled the pupil responses obtained from normal monkeys.

The data from pupil recordings in primates and humans support the hypothesis that the early transient pupil constriction under photopic conditions represents a
Photosensitive Retinal Ganglion Cells

TRANSIENT AND SUSTAINED PUPIL RESPONSE TO CHROMATIC STIMULI: PRELIMINARY RESULTS IN HUMANS

We have been exploring the pupil responses to chromatic stimuli in human subjects with normal healthy eyes and in patients with various types of neuroretinal visual loss. By using a Ganzfeld bowl as the means to provide equiluminant red and blue light, the pupil responses are tracked and recorded from a pair of lightweight eyeglasses that are integrated with miniature infrared-sensitive video cameras and worn comfortably by the patient. Figure 6 is an example of pupil recordings from a healthy adult with normal eyes who was presented a long duration (60 seconds) light stimulus, first using a long-wavelength (red bandwidth 600–620 nm) light at low, medium, and high intensities (1, 10, and 100 cd/m²) and then a short-wavelength light (blue bandwidth 465–485 nm) at similar intensities. The blue light consistently produced a larger pupil constriction amplitude compared with the red light, presumably due to the added input from intrinsic activation that occurs when a blue light is used. The difference in constriction amplitude to red light and blue light increased with increasing light intensity. At intermediate and brighter light intensities (10 cd/m² and higher), the blue light stimulus produced a sustained pupil constriction that was not seen with red light of the same photopically matched intensity. This finding is consistent with a greater intrinsic activation of melanopsin-expressing retinal ganglion cells at brighter blue light intensities, with sustained cell firing and pupil constriction dominating the response, as demonstrated in rodents and primates (15,16,33).

Given these findings in normal human eyes, we predicted that there would be a loss of pupil constriction amplitude to red light that is proportionate to the amount of cone loss in patients with isolated photoreceptor disease and a preservation of the sustained pupil constriction to bright blue light. These changes would effectively result in a greater difference of the pupil responses elicited from red light compared with blue light. Figure 7 shows the pupil recordings from such a patient with severe unilateral photoreceptor degeneration due to X-linked retinitis pigmentosa. The unilaterality is thought to be attributable to early X chromosome inactivation or a form of mosaicism. The electroretinogram (ERG) was unrecordable in the affected eye that had no light perception, and the ERG was normal in the contralateral eye with 20/20 visual acuity. The appearance of the optic nerves was normal, with no evidence of damage other than in the outer layers of the retina. Clinically, there was a >3.0 log unit relative afferent pupil defect in the affected eye. In the normal eye, there was a differential pupil response to red light and blue light similar to that shown for the normal subject in Figure 6. In the photoreceptor-degenerate eye, there was no reliable recordable pupil response to red light, even at the brightest intensity, but a blue light evoked a strong sustained pupil constriction, even though the patient perceived no light in the damaged eye.

These preliminary recordings in human subjects demonstrate that changes in the pupil responses to chromatic stimuli are readily detectable and easily quantifiable with standard instruments of clinical testing. The changes in the pupil response follow patterns that predict the underlying the ocular pathologic condition. Such results are encouraging for the development of new methods of pupil testing that may allow earlier distinction between rod and cone photoreceptor disease and retinal ganglion cell disease. We hypothesize that changes in the transient pupil response to red light and low intensity blue light may be more sensitive to cone and rod disease, whereas changes in the sustained pupil response to bright blue light may be more sensitive to optic nerve disease. Ongoing studies in our pupil laboratory are aimed to optimize stimulus conditions that elicit pupil responses that can better localize the site of damage to rods, cones, or retinal ganglion cells, quantify the extent of disease, and provide an objective reflex for monitoring the course of disease and its response to treatment.

REFERENCES

Efficacy of Corticosteroids and External Beam Radiation in the Management of Moderate to Severe Thyroid Eye Disease

Christopher I. Zoumalan, MD, Kimberly P. Cockerham, MD, Roger E. Turbin, MD, Nicholas J. Volpe, MD, Michael Kazim, MD, Raymond S. Douglas, MD, and Steven E. Feldon, MD, for the Neuro-opthalmology Research and Development Consortium (NORDIC) Thyroid Eye Disease (TED) Study Committee

Abstract: Thyroid Eye Disease (TED, Graves ophthalmopathy, thyroid orbitopathy) is the most common cause of orbital inflammation and proptosis in adults. There is no agreement on its management although corticosteroids and external beam orbital radiation (XRT) have traditionally been believed to provide benefit in active inflammation. Our review of the published literature in English disclosed an overall corticosteroid-mediated treatment response of 66.9% in a total of 834 treated patients who had moderate or severe TED. Intravenous corticosteroids used in repeated weekly pulses were more effective (overall favorable response = 74.6%, n = 177) and had fewer side effects than daily oral corticosteroids (overall favorable response = 55.5%, n = 265). A combination of corticosteroid and radiation therapy seemed to be more effective than corticosteroids alone. Our conclusions are tempered by a notable lack of standardization within and between study designs, treatment protocols, and outcome measures. Accordingly, the North American Neuro-Ophthalmology Society (NANOS), American Society of Ophthalmic Plastic and Reconstructive Surgery (ASOPRS) and the Orbital Society, in conjunction with Neuro-Ophthalmology Research and Development Consortium (NORDIC), will investigate the design and funding of a multi-center controlled trial.

Thyroid eye disease (TED, Graves ophthalmopathy, thyroid orbitopathy), which is associated with Graves disease (GD) in over 80% of cases, is an autoimmune disorder characterized by inflammation and expansion of the orbital fat and extraocular muscles. Although it has been identified in all age groups, it primarily affects adults in the fourth and fifth decades. TED can profoundly impair a patient's ability to work and perform activities of daily living. Multiple scoring systems exist to grade the activity and severity of TED. There is, however, no consensus on the most accurate system, nor is there correlation between the currently available scoring systems (1–3).

The pathophysiology of TED is not completely understood, but there is evidence for both humoral and cell-mediated immune processes (4–7). Active phase TED results from lymphocytic infiltration of the orbital and periorbital fat and muscles. The active phase generally persists for six months to three years, and is typically longer in smokers and those with prolonged hypothyroidism (8–10). The duration and severity of disease in an individual case, however, is unpredictable. After the inflammatory process ends, fibrosis and the associated disabling symptoms persist in the chronic, inactive phase.

Immunomodulatory agents are believed to affect the activity of orbital lymphocytes and fibroblasts (9,11,12).
<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients</th>
<th>Study inclusion criteria</th>
<th>Pretreatment patient profile</th>
<th>Treatment study type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bartalena et al (1983)</td>
<td>21 (36 PO steroids and XRT, 12 only PO steroids)</td>
<td>Mild to moderate active TED</td>
<td>Not clearly stated</td>
<td>Prospective case series in 36 ps that received combined PO steroids (70-80 mg tapered over 6 months) and XRT. 12 pts that received only PO steroids were part of a prospective randomized study</td>
</tr>
<tr>
<td>Bartalena et al (1998)</td>
<td>75</td>
<td>Needed to meet major categories (variations in 2 mm of proptosis and lid width, diplopia, change in vision) and minor categories (CAS, self assessment)</td>
<td>Ps with pre-existing TED given iodine and started on PO steroids 2 days after RAI</td>
<td>Prospective, randomized study, PO steroids (0.5 mg/kg/day prednisone × 1 month then with 8 wk PO taper)</td>
</tr>
<tr>
<td>Baschieri et al</td>
<td>55 (30 PO steroids, 25 IVIg)</td>
<td>Grades II–V NOSPECS (not VI)</td>
<td>Not clearly stated</td>
<td>Prospective, randomized, blinded study. 30 mg/day PO steroids × 2 wks then tapered over 5 months</td>
</tr>
<tr>
<td>Chang et al</td>
<td>22</td>
<td>Grades II–IV NOSPECS (not V and VI)</td>
<td>Not clearly stated</td>
<td>Prospective case series. IV steroids 0.5 g/day × 3 then 5 month PO steroid taper (starting at 40 mg PO/day then tapered)</td>
</tr>
<tr>
<td>Dandona et al</td>
<td>37</td>
<td>Not stated</td>
<td>Not clearly stated</td>
<td>Case series, (IV steroids 1 gm or 0.5 gm/day × 3 with three week PO oral taper)</td>
</tr>
<tr>
<td>Hiromatsu et al</td>
<td>23</td>
<td>Grades II–V NOSPECS (not VI)</td>
<td>Not clearly stated</td>
<td>Prospective case series. 1 gm/day IV steroids × 3, repeat 3–5 times over 5 weeks (total 9–12 gm) followed by 30 mg/day PO steroids × 1 month, then taper</td>
</tr>
<tr>
<td>Kahaly et al</td>
<td>70 (35 IV steroids and 35 PO steroids)</td>
<td>Defined as untreated, active, moderate TED</td>
<td>Not clearly stated</td>
<td>Randomized, single blind study. 35 received IV steroids 0.5 gm/day × 6 wks (once weekly), then down to 0.25 gm/pulse IV steroids × 6 wks (once weekly); 35 received PO steroids 0.1 gm/day then taper for 12 wks by 0.01 g/wk (cumulative dose of 4.5 gm and 4.0 gm, respectively)</td>
</tr>
<tr>
<td>Kazim et al</td>
<td>30</td>
<td>Not clearly stated</td>
<td>Not clearly stated</td>
<td>Retrospective case series. 80–120 mg/day PO steroids tapered “over many months”</td>
</tr>
<tr>
<td>Kendall-Taylor et al</td>
<td>11</td>
<td>Not clearly stated</td>
<td>2 had prior immunosuppressive treatments for TED</td>
<td>Prospective case series. IV steroid (500 mg /day × 2) then with 40 mg PO steroid taper × 4 wks</td>
</tr>
<tr>
<td>Koshiyama et al</td>
<td>8</td>
<td>Mod to severe TED</td>
<td>2 of 8 already had prior IV pulse steroids</td>
<td>Prospective case series. IV steroids 1gm/day × 3 then tapered to 30–40 mg/day PO steroids with variable tapered length (6–14 wks)</td>
</tr>
<tr>
<td>Adjunctive treatment</td>
<td>Outcome measures</td>
<td>Duration of follow up (wks)</td>
<td>Comment/Conclusions</td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>------------------</td>
<td>-----------------------------</td>
<td>---------------------</td>
<td></td>
</tr>
<tr>
<td>36 combined PO steroids and XRT (20 Gy × 2 wks)</td>
<td>Clinical activity index, clinical assessment</td>
<td>12</td>
<td>26/36 (72%) excellent or good response in combined group, 12/12 that received only PO steroids had regression or improvement in soft tissue changes, but only 33% had overall good results (no excellent results reported). Proptosis improved in 19/36 (56%) of combined group while 5/11 (45%) improved with PO alone. 5/12 (41.7%) had improvement in EOM thickness in PO group. Recurrence occurred in 4/36 (11.1%) patients in combined group.</td>
<td></td>
</tr>
<tr>
<td>CAS and patient’s impression</td>
<td></td>
<td>52</td>
<td>50/75 (67%) improved/regressed by CAS. Study showed PO steroids reduced the worsening of TED seen with RAI treatment.</td>
<td></td>
</tr>
<tr>
<td>Soft tissue changes, CT, proptosis, NOSPECS</td>
<td></td>
<td>24</td>
<td>24/30 (80%) improved diplopia with PO steroids, 18/25 (75%) with IVIG; 76% response to NOSPECS with IVIG, 66% response with PO steroids, used CT to evaluate EOM size and found an average improvement in EOM thickness in both PO and IVIG groups.</td>
<td></td>
</tr>
<tr>
<td>NOSPECS, CAS, CT</td>
<td></td>
<td>17</td>
<td>12/22 (55%) good response esp lacrimation, soreness, soft tissue swelling, proptosis; 4/10 poor responders got worse when steroids tapered to 20 mg or 10 mg/day, found that improvement in CAS correlated well with improvement seen in EOM size on CT.</td>
<td></td>
</tr>
<tr>
<td>Self assessment, eye exam, muscle size on CT</td>
<td>Not clearly stated</td>
<td>32/37 (86.5%) improved with reduction in proptosis, 6/6 that were imaged had reduction in EOM.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NOSPECS class, MRI muscle size</td>
<td></td>
<td>24</td>
<td>12/23 (52.2%) improved diplopia and soft tissue swelling, decrease in mean proptosis values, 13/23 (56.5%) decrease muscle size on MRI.</td>
<td></td>
</tr>
<tr>
<td>Proptosis and lid width, visual acuity, IOP in upgaze, diplopia, B-U/S, CAS, self assessment survey</td>
<td></td>
<td>12</td>
<td>Favorable response in 27/35 (77%) of patients receiving IV steroids vs 18/35 (51%) with PO steroids on CAS; rapid improvement seen in IV group, diplopia improved or resolved in 44% (16/35) with IV steroids, only in 4/35 (11.4%) in PO, improved motility in 16/35 (46%) in IV and 9/35 (26%) in PO. Proptosis improved in 21/35 (61%) in IV group and 14/35 (30%) in PO group. Survey: 86% satisfied with IV vs 54% in PO. No PO steroid taper used for IV pulse steroids. Found a more significant improvement in EOM thickness via B-U/S in patients that received IV than PO steroids.</td>
<td></td>
</tr>
<tr>
<td>Subjective improvement, improved fusion, proptosis, clinical exam</td>
<td></td>
<td>24</td>
<td>10/30 (33%) improved in some way. Proptosis and diplopia improved in 10/30 (33%); 6/16 with optic neuropathy improved, though 9 underwent additional treatment (XRT of surgical decompression). One patient noted to have recurrence.</td>
<td></td>
</tr>
<tr>
<td>Eye exam with IOP, CT EOM size, photos</td>
<td></td>
<td>24</td>
<td>6/7 (85.7%) with optic neuropathy improved, 9/11 (81.8%) improved soft tissue swelling, proptosis persisted in all patients, 8/9 (88.9%) improved EOM size on CT; of note, the 3 poor responders had TED &gt; 1 year, 9 had CT’s performed and 8 had a reduction of EOM size, though variable.</td>
<td></td>
</tr>
<tr>
<td>XRT (20 Gy × 2 wks) given after completion of pulse IV steroids</td>
<td>Diplopia, muscle size on MRI, NOSPECS</td>
<td>3 yr (156 wks)</td>
<td>5/8 (62.5%) with eliminated diplopia, NOSPECS index improved on average, 6/8 (75%) decreased EOM size on MRI (EOM size compared with optic nerve thickness), 7/8 (88%) excellent result, no recurrence seen.</td>
<td></td>
</tr>
<tr>
<td>Authors</td>
<td>Patients</td>
<td>Study inclusion criteria</td>
<td>Pretreatment patient profile</td>
<td>Treatment study type</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------------------------------</td>
<td>----------------------------------------------------------------</td>
<td>-------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Macchia et al⁹²</td>
<td>51 (26 PO steroids and 25 IV steroids)</td>
<td>Not clearly stated</td>
<td>None received prior treatment for TED</td>
<td>Randomized, prospective study 60–80 mg PO steroids with 4–6 month taper. IV group received 1000 mg/day for two consecutive days each week for total of 6 weeks</td>
</tr>
<tr>
<td>Marcocci et al (1987)³⁴</td>
<td>60 (30 XRT and PO steroids, 30 combined XRT and retrobulbar steroids)</td>
<td>Not clearly stated</td>
<td>Not clearly stated</td>
<td>Prospective, randomized, controlled study. PO steroids group: 70–80 mg/day PO steroids × 3 wks then tapered over 5–6 months, Retrobulbar steroids group: 14 injections (methylprednisolone, 40 mg/1.5 mL) q20–30 days × 9 months</td>
</tr>
<tr>
<td>Marcocci et al (2001)³⁰</td>
<td>82 (41 PO steroids, 41 IV steroids)</td>
<td>Not clearly stated</td>
<td>12 received prior immunosuppressive treatment, 1 with prior orbital decompression</td>
<td>Prospective, single blind, randomized study, 100 mg/day PO steroid with taper over 22 wks, (total dose 6 g) vs IV steroids 15 mg/kg/day × 2 days every 2 weeks for 4 cycles, repeat with 7.5 mg/kg IV steroids × 2 every 2 wks for 4 cycles (total dose 9–12 gm)</td>
</tr>
<tr>
<td>Matejka et al¹⁷</td>
<td>8</td>
<td>Ophthalmology Index &gt; 8 on NOSPECS</td>
<td>Not clearly stated</td>
<td>Prospective case series. IV 12.5 mg/kg q 1 mo, then repeated 3–6 times monthly, given PO steroids interpulse (0.5 mg/kg/day) then 4 wk PO steroid taper after last pulse IV dose</td>
</tr>
<tr>
<td>Noth et al¹⁵</td>
<td>19</td>
<td>Not clearly stated</td>
<td>No clearly stated</td>
<td>Prospective case series. 20–60 mg/day PO steroids × 3 months</td>
</tr>
<tr>
<td>Prummel et al (1989)²⁸</td>
<td>18</td>
<td>Severe NOSPECS (Grade II–VI)</td>
<td>Not clearly stated</td>
<td>Prospective, single blind, randomized study. 60 mg PO steroids/day vs cyclosporine × 12 wks</td>
</tr>
<tr>
<td>Prummel et al (1993)¹²</td>
<td>56 (28 PO steroids, 28 XRT)</td>
<td>Severe NOSPECS (Grade II–VI)</td>
<td>None received prior treatment for TED</td>
<td>Prospective, double blind randomized trial. 60 mg PO steroids/day for 4 wks then taper down over 20 wks</td>
</tr>
<tr>
<td>Staar et al⁸⁰</td>
<td>225</td>
<td>NOSPECS 2–6, and orbitopathy index</td>
<td>187 received prior immunosuppressive (steroid) treatment</td>
<td>Partly retrospective and prospective case series. 60 mg PO steroids simultaneously started with onset of XRT, PO steroids tapered over 6 wks</td>
</tr>
<tr>
<td>Tagami et al⁸⁰</td>
<td>27 (11 XRT and IV steroids, 16 only IV steroids)</td>
<td>Not clearly stated</td>
<td>Not clearly stated</td>
<td>Prospective case series. 1 gm/pulse IV steroids × 3, repeat q1 week × 4 (if clinically indicated), then followed by 40–50 mg/day PO steroids, tapered over next 3–12 months</td>
</tr>
</tbody>
</table>

CAS, clinical activity score; RAI, radioactive iodine treatment; XRT, external beam orbital radiation; TED, thyroid eye disease; PO, oral; (grade 1), soft tissue involvement with symptoms and signs (grade 2), proptosis (grade 3), extraocular muscle involvement (grade 4), corneal...
### Adjunctive Treatment

<table>
<thead>
<tr>
<th>Adjunctive Treatment</th>
<th>Outcome Measures</th>
<th>Duration of Follow Up (wks)</th>
<th>Comment/Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>NOSPECS, self assessment survey, proptosis</td>
<td>2 yrs</td>
<td>21/25 (84%) had improvement with IV steroids, and 15/26 (57%) had improvement with PO steroids. Proptosis improved similarly in both groups. Four patients that received PO steroids had to withdraw therapy due to severe side effects. No recurrences were seen in a two-year follow up.</td>
</tr>
<tr>
<td>XRT (20 Gy × 2 wks), started at same time as steroids</td>
<td>Clinical exam, NOSPECS</td>
<td>78</td>
<td>19/30 (63%) improvement of EOM with PO steroids and XRT, overall excellent response in 18/30 (60%). Retrobulbar steroid and XRT group had overall improvement in 80%, 39% improvement in proptosis, and 17% improvement of EOM.</td>
</tr>
<tr>
<td>XRT (20 Gy × 2 wks) started one week after onset of steroids</td>
<td>Proptosis, lid fissure width, diplopia, CAS</td>
<td>52</td>
<td>Overall improvement of 36/41 (88%) with IV steroids, (26/41) 63% with PO steroids; less side effects with IV (23/41 vs 35/41 in PO), CAS more improved with IV (36/41 vs 26/41 in PO); diplopia improved in 14/40 in IV, 12/40 in PO; optic neuropathy better result with IV (11/14 vs 3/9); no PO steroid taper used in IV steroids group.</td>
</tr>
<tr>
<td>+/− XRT (20 Gy × 2 wks)</td>
<td>Clinical exam, NOSPECS</td>
<td>~3 yrs (156 wks)</td>
<td>5/11 (45.5%) had good result with PO steroids only, 6 went on to have XRT and I went on to have XRT and decompressive surgery.</td>
</tr>
<tr>
<td>Vs Cyclosporine</td>
<td>NOSPECS, proptosis, EOM size on CT</td>
<td>52</td>
<td>11/18 (61.1%) responded by EOM size on CT, clinical scores and proptosis at 12 wks; in non responders, combination with cyclosporine was helpful, followed for 52 wks but eventually 17/36 had surgery or XRT.</td>
</tr>
<tr>
<td>Vs XRT (20 Gy × 2 wks)</td>
<td>Highest NOSPECS class, CT</td>
<td>24</td>
<td>14/28 (50%) responded to steroids, 13/28 (46%) responded to XRT, both had similar improvement in EOM size on CT, XRT seemed to improve motility more than PO steroids. Soft tissue swelling improved better with PO steroids than XRT.</td>
</tr>
<tr>
<td>XRT (16–19 Gy over 6 wks)</td>
<td>Subjective impression, NOSPECS</td>
<td>52</td>
<td>Overall, 153/225 (68%) improved. Proptosis improved in 131/207 (64%), and diplopia improved in 133/169 (78.7%). 72/225 (32%) eventually had orbital decompressive surgery over the course of the year follow up due to progression/recurrence.</td>
</tr>
<tr>
<td>12 pts received XRT (followed 2 wks after pulse IV steroids were completed)</td>
<td>Clinical score, CT or MRI of EOM, NOSPECS</td>
<td>2 yrs (104 wks)</td>
<td>21/27 (77.8%) diplopia improved (all pts had diplopia) or disappeared; overall 9/11 (81.8%) improved in XRT and IV steroids group, and 12/16 (75%) improved in IV steroids group. 15/27 (55.6%) improved proptosis; NOSPECS improved as average across the group; used CT to compare EOM size (by comparing the thickness to optic nerve) and found a correlation in EOM and NOSPECS improvement in responders.</td>
</tr>
</tbody>
</table>

IV, intravenous; IVIg, intravenous immunoglobulin therapy; EOM, extraocular muscles; NOSPECS, no signs or symptoms (grade 0), only signs involvement (grade 5), and sight involvement (grade 6).
The most commonly employed immunomodulators include corticosteroids with or without adjunctive external beam orbital radiation (XRT) in moderate to severe cases of TED. However, disease management varies widely (13). The goals of medical therapy are to shorten the duration and minimize the severity of the active phase, thereby reducing the chronic phase disfigurement and disability produced by irreversible fibrosis.

Corticosteroids are typically administered orally or intravenously (IV). Local injections of corticosteroids into the orbit have failed to provide an effect in improving orbitopathy (14,15). Some studies have shown that local injections can improve motility and extraocular muscle (EOM) size and can be a suitable alternative to patients with contraindications to systemic corticosteroids (16,17).

XRT was first used empirically to treat TED. While the mechanism for its action is not fully understood, radiation (XRT, typical total dose = 20 Gy) is biologically active against infiltrating lymphocytes, tissue-bound monocytes, and fibroblasts so as to alter the local cellular matrix and interrupt the inflammatory process in a more permanent fashion than can be achieved with corticosteroids (14,18). One recent prospective, double-masked, sham-controlled clinical trial produced more debate than consensus regarding the efficacy of XRT therapy for TED (19,20).

There is no agreement on the management of TED (18,21,22). As an alternative to corticosteroids and XRT, other immunomodulatory agents such as azathioprine, cyclosporine, intravenous immunoglobulin (IVIg), and plasmapheresis have been used, but they play a more limited role (23–28). Efficacy studies have not been well modeled, and are mainly small, retrospective, or uncontrolled (18,21,22,29,30). Interpretation of the data from the existing studies is limited by the lack of good natural history data and the highly variable nature of the disease. We have evaluated the relevant publications in the English language to compare the outcomes of TED patients treated with corticosteroids and/or XRT.

**RESULTS**

**Study Profiles**

We identified nineteen studies for our review. Seven had enrolled patients in randomized prospective studies (12,14,28,30–33); the remainder were either prospective or retrospective case series.

**General Patient Treatment Profile**

A total of 834 patients from nineteen studies were reviewed. Study patient populations were dissimilar, and inclusion and exclusion criteria varied. In particular, some studies excluded patients who had had prior treatment for TED (12,14,31–34). Others included patients that had already been treated with XRT, immunomodulatory agents, or decompressive surgery (21,28,30,35–40). Still others failed to detail prior treatment (41–44). The study of Marcocci et al (30) was the only one that detailed the thyroid metabolic status of the patients such that 81 (99.8%) of 82 patients presented with hyperthyroidism and TED; one patient had euthyroid TED.

Of the 834 patients, 597 (71.6%) from 13 studies were treated with oral corticosteroids with or without XRT. Of the 597 patients, 265 had received only oral prednisone (average of 76 +/- 26 mg/day). The length of oral corticosteroid treatment (including taper) averaged 17.5 +/- 5.4 weeks. In 10 studies, 237 patients (28.4%) were treated predominantly with IV corticosteroids (methylprednisolone) with or without XRT. Seven of these studies mainly used 1000 mg/pulse and the remaining three studies used a 500 mg/pulse. The average number of pulses received was 5.8 +/- 3.8 over an average length of 13 +/- 1.5 weeks of treatment. Most of the patients who had received IV corticosteroids (n = 177) without XRT had also received oral corticosteroids between pulses of IV corticosteroids and were given a tapered course of oral corticosteroids that averaged 37.9 +/- 4.9 mg/day over 14 +/- 17 weeks. The follow-up interval for all studies averaged 59 weeks (range 12 weeks to 3 years) (Table 1).

**Clinical Measurement of Disease Severity and Treatment Response**

TED severity and activity were assessed using different scoring systems, including the NOSPECS classification system (No signs or symptoms [grade 0]; Only signs [grade 1]; Soft tissue involvement with symptoms and signs [grade 2]; Proptosis [grade 3]; Extraocular muscle involvement [grade 4]; Corneal involvement [grade 5]; Sight involvement [grade 6]), American Thyroid Association classification, Stanford Score, International Index, clinical activity score (CAS), and self-assessment surveys. Other data came from the clinical examination findings, including proptosis, gaze-evoked changes in intraocular pressure (IOP), and from neuroimaging abnormalities.

**METHODS**

We performed a review of published studies identified in a PubMed on-line review from January 1966 to July 2006 using the following key words: Graves ophthalmopathy, thyroid eye disease, Graves disease, and thyroid orbitopathy. Inclusion criteria required at least eight enrolled subjects within a retrospective or prospective study published in the English language. Our review compared the outcomes of using corticosteroids with or without XRT. We included only those studies that compared the outcomes through definable measurements, orbital imaging studies (CT or MRI), self-assessment surveys, or clinical examinations.
The NOSPECS classification system was most commonly used (12 of 19 studies). It documents the presence of specific symptoms and signs of which only some are characteristic of active disease. The CAS was used in 6 of 19 studies. It takes into account seven clinical measurements and assigns a point to each symptom or sign (retrobulbar pain, pain on eye movements, eyelid edema, conjunctival injection, chemosis, swelling of the caruncle, eyelid edema or fullness). Many studies included self-assessment patient surveys (Table 1).

**Neuroimaging**

Ten studies employed neuroimaging to measure the outcome of TED treatment (12,28,33,34,36–38,40,42,44). CT, MRI, and B-ultrasound were used to evaluate EOM size. There was no standardized grading protocol (Table 1). All studies showed an overall improvement in EOM thickness or proptosis after oral or IV corticosteroid treatment with and without the use of external beam radiation (x-irradiation, XRT). The degree of improvement correlated well with the overall favorable response reported by clinical measures. Matejka et al (37) measured the amount of proptosis on CT and found an overall improvement in all eight patients who had received predominantly IV corticosteroids. The study of Hiromatsu et al (44) was unique in using MRI to judge response in TED. Baschieri et al (34) found reduction in EOM thickness on CT after oral prednisone 80 mg/day for a total two weeks with a five month taper. One of the studies employed B-ultrasound to note significant greater reduction in EOM thickness in patients who had received IV corticosteroids than in those who had received oral corticosteroids (33).

**Intravenous vs. Oral Corticosteroids**

Because of dissimilar assessment measures within and among studies, treatment outcomes are reported in relation to each study’s outcome measures. We judged the results as favorable if the author reported the results as either good or excellent.

Corticosteroids were the primary medical therapy used to treat active TED. There was an overall 66.9% favorable response to corticosteroid treatment among all 834 patients, which included those that may also have been treated with XRT. A total of 442 patients were treated with oral or predominantly IV corticosteroids alone. A total of 151 (55.5%) of 265 patients treated with oral corticosteroids alone had a favorable response, and 132 (74.6%) of 177 patients treated with IV corticosteroids alone had a favorable response.

Patients who had received predominantly IV corticosteroids seemed to have greater improvement in diplopia, ocular motility, and proptosis than those who had received only oral corticosteroids. But patients who received only oral corticosteroids showed a greater improvement in EOM thickness than patients who received predominantly IV corticosteroids (Table 2).

Two prospective randomized studies compared IV to oral corticosteroid treatment (30,32,33). Neither of these studies used a tapered regimen of oral corticosteroids followed a regimen of IV corticosteroids. Kahaly et al (33) showed an improvement in the CAS in 27 (77%) of 35 patients treated with IV corticosteroids as compared to 18 (51%) of 35 patients treated with oral corticosteroids. Based on a self-assessment survey, 80% of patients receiving IV corticosteroids as compared to 54% receiving oral corticosteroids were satisfied with the treatment results and had an improved quality of life. Macchia et al (32) reported similar results, such that 21 (84%) of 25 patients treated with IV corticosteroids had a favorable response as compared to 15 (57%) of 26 treated with oral corticosteroids. However, proptosis improved equally among both groups.

**Combined Corticosteroid and XRT Treatment**

The cumulative radiation dose and the radiation field were similar in nearly all studies (Table 1). A total of 20 Gy

<table>
<thead>
<tr>
<th>TABLE 2. Outcomes following treatment of patients with active thyroid eye disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>Total patients</td>
</tr>
<tr>
<td>Overall favorable response</td>
</tr>
<tr>
<td>Improvement in diplopia</td>
</tr>
<tr>
<td>Improvement in motility</td>
</tr>
<tr>
<td>Improvement in proptosis</td>
</tr>
<tr>
<td>Improvement in extraocular muscle thickness</td>
</tr>
</tbody>
</table>

Cort, corticosteroid; XRT, external beam x-irradiation; IV, intravenous administration; PO, oral administration.
was delivered to each orbit over a period of two weeks. There was an overall 70.2% favorable response in the 392 patients who underwent both XRT and IV or oral corticosteroid treatment. Compare this to an overall 64.0% favorable response in the 442 patients who received IV or oral corticosteroids without XRT. More specifically, 223 (67.2%) of 332 patients who received oral corticosteroids and XRT (14,21,30,35,39) responded favorably as compared to 52 (86.7%) of 60 patients who received predominantly IV corticosteroids and XRT (30,36,40) (Table 2).

One prospective randomized study compared the outcome following IV corticosteroids and XRT to the outcome following oral corticosteroids and XRT. Marcocci et al (30) found a significantly greater short-term improvement of periorcular edema, erythema, orbital ache, and ocular motility in patients who had received IV corticosteroids and XRT (88%) when compared to oral corticosteroids and XRT (63%). Proptosis improved in 19 (47.5%) of 40 patients receiving IV corticosteroids and XRT and in 16 (40%) of 40 patients receiving oral corticosteroids and XRT. Optic neuropathy improved in 13 (92%) of 14 patients after treatment with IV corticosteroids and XRT, but only in 3 (33%) of 9 patients who received oral corticosteroids and XRT. This difference, however, was not statistically significant (30).

**Intravenous vs. Oral Corticosteroid Treatment With or Without Adjunctive XRT**

Overall, treatment with pulsed IV corticosteroids was more effective and better tolerated than chronic treatment with oral corticosteroids alone. Oral corticosteroids produced a favorable response in 62.6% of patients with or without the use of XRT (n = 597). This compares to a favorable response in 77.6% of patients treated with IV corticosteroids with or without XRT (n = 237). In the studies reporting results, the patients who received predominantly IV corticosteroids showed greater improvement in diplopia, ocular motility, and proptosis in comparison to those who received oral corticosteroids with or without adjunctive XRT. In contrast, the patients who received oral corticosteroids showed a greater improvement in EOM thickness in comparison to the patients who received predominantly IV corticosteroids with or without adjunctive XRT (Table 2).

**Corticosteroid Side Effects**

There was a higher rate of side effects to corticosteroids administered via the oral route than to corticosteroids administered via the IV route. Chronic oral corticosteroid treatment was associated with Cushingoid facies, weight gain, osteoporosis, gastric irritation, labile hypertension, elevated intraocular pressure, elevation in blood sugar, and mood alteration. Marcocci et al (30) documented that 35 (85.4%) of 41 patients treated with an approximately six-month oral corticosteroid taper (starting at 100 mg prednisolone by mouth daily for a cumulative dose of 6 grams) demonstrated side effects including weight gain, urinary tract infections, transient hyperglycemia, and decreased bone mineral density. Three patients who had received oral steroids in the randomized study of Macchia et al (32) had to withdraw from their treatment due to “severe signs or symptoms of hypercortisolism.” Prummel et al (12) found that 25 of 28 patients who received a 20-week oral corticosteroid taper (starting at 60 mg prednisolone by mouth daily for four weeks followed by a taper) experienced only minor side effects. One patient developed depression and a second patient manifested a recurrent herpetic zoster eruption. Baschieri et al (34) reported two cases of hemorrhagic gastritis in patients receiving 80 mg prednisone by mouth daily with a 5-month taper. One patient developed bipolar disorder. More frequent side effects included Cushingoid facies (5 out of 30 patients) and abnormal glucose tolerance (5 out of 30 patients).

Intravenous corticosteroid treatment was associated with a lower rate of adverse side effects. Kahaly et al (33) reported adverse events in only 6 (17%) of 35 patients, including weight gain, insomnia, palpitations, and gastrointestinal discomfort. However, Marcocci et al (30) reported adverse effects in 23 (56.1%) of 41 patients, including urinary tract infections and impaired glucose tolerance. Nine patients inexplicably had a mean percentage increase in bone mineral density after IV corticosteroid treatment. One patient had transient elevation of serum aminotransferase levels (34).

**Radiation Side Effects**

Radiation was well tolerated and produced few short-term side effects. Koshiyama et al (36), Marcocci et al (30), Staar et al (39), and Prummel et al (12) reported no side effects from radiation. In the study of Bartalena et al (21), with a follow-up over 26 months, there were no new cataracts. However, Prummel et al (12) found that 15 (54%) of 28 patients surveyed had side effects, usually minor, including transient hair loss at temples, tiredness, myalgias, headaches, insomnia, and nausea.

**Reactivation of TED After Treatment**

Seven of the reviewed studies addressed the incidence and timing of disease recurrence after successful initial treatment (21,32,35,36,39,42,43). The study of Koshiyama et al (36) found no recurrence of TED among all eight patients who had received predominantly IV corticosteroids and combined XRT after a three-year follow-up. The study of Macchia et al (32) found no
recurrence of TED among 51 patients who had received either oral (n = 26) or IV corticosteroids (n = 25). However, four other studies reported substantial recurrence in treated patients. Chang et al (42) reported that 4 of 10 patients worsened when the oral corticosteroids were discontinued or quickly tapered to 20 mg/day over a course of five months. Noth et al (35) documented that 12 (63.2%) of 19 patients followed for three years required further immunosuppressive therapy and XRT due to disease recurrence or progression. Staar et al (39) also reported that because of disease progression or recurrence, 72 (32%) of 225 patients eventually proceeded to orbital decompressive surgery after a year’s treatment with a combination of oral corticosteroids and XRT.

Summary of Outcomes

A review of the published literature in English has suggested that corticosteroid-mediated treatment produces benefit in 66.9% in TED patients who have moderate to severe disease. IV corticosteroids used in repeated daily or weekly pulses (average of 5.8 pulses/treatment epoch) were more effective than daily oral corticosteroids. Intravenous administration of corticosteroids appeared to be more effective than oral administration alone. A combination of corticosteroids and XRT was more effective than corticosteroids alone. In combination with XRT, IV administration of corticosteroids was more effective than oral administration.

Intravenous corticosteroids were associated with fewer side effects than oral corticosteroids. However, single case reports not included in this series have reported fatal cardiac and fatal hepatic necrosis with the use of IV corticosteroids for TED (45,46).

XRT appeared to be well tolerated with few if any side effects. However, a report by Gorman et al (20), not included in this review, discovered newly dilated capillaries or microaneurysms on fluorescein angiograms or fundus photographs in five eyes among 3 of 37 treated patients three years after receiving XRT.

Among the three prospective randomized studies, IV corticosteroids had a clear benefit in treatment outcome over oral corticosteroids (30,32,33). Patients treated with IV or oral corticosteroids showed improvement in proptosis, diplopia, ocular motility, and in self-assessment of benefit, but the treatment outcomes were more substantial in those treated with IV corticosteroids (over 77% favorable outcome) than with oral corticosteroids (up to 62% favorable outcome). The only study (12) that compared oral corticosteroid administration to XRT in a prospective, double-blind randomized trial showed similar treatment outcomes (self-assessment, EOM size on CT), but XRT seemed to improve ocular motility more than did oral corticosteroids, while oral corticosteroids seemed to improve soft tissue swelling more effectively.

Cautions

Caution is warranted regarding the interpretation of outcomes in the studies we have reviewed. The studies differed in design, treatment protocol, and outcome measures. The potential clinical impact of corticosteroids and XRT in the treatment of TED was difficult to assess reliably. These studies provide little insight regarding pathophysiology or effect of treatment on quality of life.

It was particularly difficult to interpret the results of TED severity and activity among different scoring systems. NOSPECS was the most commonly used scoring system yet it documents manifestations not always characteristic of active disease. Clinical worsening may not represent increased inflammatory activity but rather progressive fibrosis associated with resolving inflammation. CAS, another scoring system used in several of the studies reviewed, does not provide information regarding overall progression or severity of TED. Self-assessment surveys used to document improvements in quality of life are non-standardized and difficult to interpret across studies. The identification of active TED remains an imperfect combination of the patient’s impression and the clinician’s interpretation of the physical signs.

We conclude that there is inadequate case-based evidence to ascertain reliably whether medical therapy with corticosteroids or XRT shortens the active phase of disease or improves long-term disfigurement and disability in patients with moderate to severe TED. To answer this question more rigorously, the North American Neuro-Ophthalmology Society (NANOS), American Society of Ophthalmic Plastic and Reconstructive Surgery (ASOPRS), and the Orbital Society, working in conjunction with Neuro-Ophthalmology Research and Development Consortium (NORDIC), have established a committee to pursue the design and funding of a large, multi-center, double-masked, placebo controlled study.

REFERENCES

1. Gorman CA. The measurement of change in Graves’ ophthalmopathy. Thyroid 1998;8:539–43.


Thrombolysis for Central Retinal Artery Occlusion

Valérie Biousse, MD, Olivier Calvetti, MD, Beau B. Bruce, MD, and Nancy J. Newman, MD

Abstract: Central retinal artery occlusion (CRAO) frequently causes severe and irreversible visual loss. For many years, various conservative treatments have been proposed for acute CRAO, but their efficacy remains unproven. Over the past 20 years, CRAO has also been treated with thrombolytic agents administered intravenously or intra-arterially. However, all thrombolytic studies are retrospective and uncontrolled, so that the benefit of this treatment remains uncertain. A prospective controlled clinical trial is ongoing in Europe and should provide more reliable information. Even if this trial demonstrates a benefit, thrombolytic treatment is unlikely to become widespread in the management of CRAO unless it can be deployed quickly after the event.

METHODS

English and non-English language articles were retrieved using a keyword search of Medline. Search terms included “central retinal artery occlusion,” “thrombolysis,” and “fibrinolysis.” This search was supplemented by manually searching the reference lists of all articles. All reports of thrombolysis in CRAO were included. Cases of branch retinal artery occlusions (BRAOs) were excluded. Although many of these articles were case reports and 19 articles were not written in English, all were included in our review. Articles were translated from French, German, Japanese, Chinese, Spanish, and Italian. As an exception, only the abstract in English was reviewed for one article in Czech (39).

Information on study design, outcome, and analyses was documented in a standardized data extraction form. Information entered included 1) year of publication, 2) country of origin, 3) number of patients treated, 4) study design, 5) modalities of thrombolytic treatment [IV or intra-arterial with selective catheterization of the internal carotid artery (ICA) and its branches, type and dose of thrombolytic agent used], 6) delay between onset of CRAO and thrombolysis, 7) visual outcome, and 8) complications. Two investigators (VB and OC) reviewed the articles independently.

A total of 35 articles (including a meta-analysis published in 2000) (51) were included in this review. Other review articles and meeting abstracts were not included.
### TABLE 1. “Conservative” treatments proposed for the treatment of acute central retinal artery occlusion

<table>
<thead>
<tr>
<th>Goal</th>
<th>Proposed treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dislodge an embolus from the central retinal artery</td>
<td>Ocular massage&lt;br&gt;Nd:YAG laser (0.5—1.0 mJ) (attempt to lyse the embolus)<em>&lt;br&gt;Surgical removal of clot from the central retinal artery (vitrectomy, vessel cannulation, and thrombus disruption)</em></td>
</tr>
<tr>
<td>Reduce intraocular pressure and increase retinal blood flow</td>
<td>Ocular massage&lt;br&gt;Anterior chamber paracentesis&lt;br&gt;Topical glaucoma medications&lt;br&gt;Acetazolamide (250–500 mg IV)&lt;br&gt;Mannitol (IV)&lt;br&gt;Glycerol (PO)</td>
</tr>
<tr>
<td>Vasodilation of ocular blood supply</td>
<td>Calcium channel blockers (PO or IV)&lt;br&gt;Prostaglandin E1 (IV) (potent vasodilator of the microcirculation or capillary system used to treat patients with peripheral vascular disease)&lt;br&gt;Sublingual nitroglycerin (rapid acting vasodilator used for acute coronary syndromes)&lt;br&gt;Retrobulbar injection of papaverine (vasodilator, inhibitor of phosphodiesterase) or tolazoline (vasorelaxant, nonselective adrenoreceptor blocker)</td>
</tr>
<tr>
<td>Improve retinal circulation</td>
<td>Pentoxifyllin (oral agent used in systemic vascular diseases to improve perfusion of occluded vessels by increasing red blood cell deformability, reducing blood viscosity, and decreasing the potential for platelet aggregation and thrombus formation)&lt;br&gt;Hemodilution (based on the observation that reducing hematocrit levels lowers plasma viscosity, which may lead to improved retinal circulation and perfusion)</td>
</tr>
<tr>
<td>Reduce retinal edema</td>
<td>Methylprednisolone IV&lt;br&gt;Hyperbaric oxygen&lt;br&gt;Anticoagulants (heparin IV acutely)&lt;br&gt;Antiplatelet agents</td>
</tr>
<tr>
<td>Maintain retinal oxygenation until spontaneous reperfusion</td>
<td></td>
</tr>
<tr>
<td>Act on the thrombus</td>
<td></td>
</tr>
</tbody>
</table>

*Although YAG laser and surgery are invasive treatment modalities, we kept them in this table because they were considered by previous authors to be “conservative treatments,” and they differ from thrombolysis.

The main outcome reported in these studies was improvement in visual acuity from baseline at the completion of the follow-up period. Other outcomes reported in some studies were improvement of the visual field from baseline at the completion of the follow-up period, and evidence of revascularization of retinal arteries on retinal fluorescein angiograms performed before and after thrombolysis. Because only a few studies reported results of visual field tests and fluorescein retinal angiograms and because reperfusion of the central artery on a fluorescein angiogram is meaningless if not accompanied by measures of visual function, we recorded visual acuity as the primary indicator of outcome. We specifically noted when the authors mentioned a “complete visual recovery” or major improvement in visual acuity from baseline to after thrombolytic administration, arbitrarily categorized into “improved visual acuity by at least 8 Snellen lines or 4 Snellen lines.”

For each study for which data were available, the pretreatment visual acuity, post-treatment visual acuity, and treatment delay were recorded. Visual acuity data were converted to logMAR units, and a difference between post- and pretreatment acuity was calculated. Linear regression
IS CRAO LIKE ANY OTHER STROKE?

CRAO leads to irreversible retinal infarction if the retinal blood flow is not restored rapidly. The diagnosis is easily made clinically in a patient presenting with acute visual loss, an ipsilateral relative afferent pupillary defect, retinal edema with attenuation of the retinal arteries, and a cherry red spot (Figs. 1-3). Visual acuity at the initial presentation is usually very poor, with 90% of patients having no better than finger counting vision (3). A classification of CRAO in 3 stages is based on the severity of visual acuity loss at presentation and on fundus appearance (Table 2). This classification is useful for the prognosis of acute CRAO (4,53,66). Approximately one-third of human eyes have a patent cilio-retinal artery that may allow for preserved central visual acuity when the cilio-retinal artery supplies the foveal region in patients with CRAO (4,67-69). Retinal arterial emboli are seen in up to 20%-40% of patients with acute CRAO (2,3) and are believed to originate mostly from the ICA, although all causes of cerebral infarction have also been reported to cause CRAO.

The natural history of CRAO remains a subject of debate. The largest series evaluating the outcome of CRAO included 171 eyes with nonarteritic CRAO and no cilio-retinal artery sparing (4). It showed that 22% of patients who initially presented with visual acuity of count fingers had improved visual acuity at follow-up. Other authors have suggested that between 14% (7) and 35% (5) of patients with CRAO improve with conservative treatments. Rare patients with spontaneous complete recovery have also been reported (70).

The central retinal artery is a branch of the ophthalmic artery, which arises from the intracranial ICA. Hence, an ocular infarction from central retinal or ophthalmic artery occlusion is appropriately considered an infarction in the anterior circulation territory. This concept is well illustrated by data accumulated on the risk of ipsilateral cerebral infarction after an episode of transient retinal ischemia (transient monocular visual loss or retinal transient ischemic attack [TIA]) (71). The North American Symptomatic Carotid Endarterectomy Trial (NASCET) has shown this stroke risk to be approximately 10% after 3 years for patients with ipsilateral atherosclerotic carotid artery stenosis (72,73). However, the same study also showed that the risk of cerebral infarction after a retinal TIA is much lower than that after a hemispheric TIA (73).

This NASCET finding is probably related to the anatomy of the ophthalmic artery, which branches off the ICA at an angle of 90°. Why would emboli take a 90° turn instead of simply flowing distally into one of the intracranial branches of the ICA? Interestingly, two studies (74,75) showed that retinal ischemia is caused more often by carotid stenosis than by a cardiac source of emboli. The authors explained this observation by rheologic phenomena in which very small emboli from carotid stenosis tend to stick to the carotid wall and may therefore be more likely to make a 90° turn if they happen to flow by the ophthalmic artery origin, whereas larger emboli originating in the heart are localized in the center of the flowing blood and have a tendency to be pushed more distally into the intracranial circulation (74).

The risk of CRAO after a retinal TIA is not reliably known; it is estimated to be only 1% per year (76). Therefore, although there is no doubt that CRAO is an ischemic stroke in the anterior circulation, it seems to differ from most cerebral infarctions.

CRAO also differs from other stroke in being far less common. Non-CRAO stroke is the third leading cause of death and one of the leading causes of disability in North America, Europe, and Asia. Stroke costs now exceed $45 billion per year. These numbers justify the numerous randomized stroke trials and the recommendations for aggressive secondary stroke prevention. On the other hand, the annual incidence of CRAO is only about 0.85 per 100,000 (25). In addition, the mortality of acute CRAO is minimal, with a morbidity based mostly on whether affected patients have a normally sighted fellow eye. Therefore, unless CRAO occurs in the only sighted eye, the cost of CRAO cannot be considered equivalent to the cost of stroke in general.

HOW SHOULD CRAO BE MANAGED?

Should Patients With CRAO be Admitted Immediately for Observation and Workup?

Patients with sudden monocular visual loss rarely present to the emergency room acutely. In most cases, they are evaluated by a community optometrist, ophthalmologist, or primary care physician and subsequently are referred to a specialist who will make the diagnosis. With this delay in diagnosis, it is too late for any effective treatment.

Natural history data suggest that in cerebral infarctions and cerebral TIAs, the risk of recurrent infarction is highest within the first few days after the first ischemic event. Given that patients with CRAO typically present to physicians several days after the event, it is reasonable to recommend that the etiologic workup be obtained promptly but on an outpatient basis. This workup is often best facilitated by the primary care physician, who can also immediately begin treatment for secondary prevention of cerebral infarction and cardiovascular disease. The only real emergency in this setting is to rule out giant cell arteritis in patients older than 50 years.
### TABLE 2. Classification of central retinal artery occlusion

<table>
<thead>
<tr>
<th>Stage 1: Incomplete CRAO</th>
<th>Figure 1: Stage 1 CRAO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased visual acuity</td>
<td></td>
</tr>
<tr>
<td>Mild retinal edema</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage 2: Subtotal CRAO</th>
<th>Figure 2: Stage 2 CRAO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severely decreased visual acuity</td>
<td></td>
</tr>
<tr>
<td>Marked retinal edema</td>
<td></td>
</tr>
<tr>
<td>Cherry red spot</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage 3: Total CRAO</th>
<th>Figure 3: Stage 3 CRAO*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vision reduced to no light perception</td>
<td></td>
</tr>
<tr>
<td>Massive retinal edema</td>
<td></td>
</tr>
<tr>
<td>Cherry red spot may be absent</td>
<td></td>
</tr>
</tbody>
</table>

CRAO, central retinal artery occlusion.
Adapted from Schmidt and Schumacher (66) and from Hayreh and Zimmerman (4).
*The presence of cilioretinal artery sparing, shown in Figure 3, should be noted in all cases.
On rare occasions, a patient with CRAO will be evaluated within a few hours of visual loss. In theory, these patients have the highest risk of recurrent ischemia and cerebral infarction and may be good candidates for acute treatment of retinal infarction. They should be admitted for observation, treatment, and immediate workup.

Patients younger than 50 years, in whom a CRAO is extremely unusual and often points to an underlying systemic vascular disorder, should be admitted for observation and workup even if their presentation is delayed. Indeed, the likelihood of discovering an ICA dissection, a systemic vasculopathy, a cardiac abnormality, or a coagulopathy is very high in the young patient with acute CRAO.

Should the Workup for CRAO be Similar to That for Other Stroke?

Patients older than 50 years presenting with an acute or subacute CRAO need to be evaluated on an emergency basis for giant cell arteritis. Once giant cell arteritis is ruled out, it is appropriate to obtain the same workup as for patients with a cerebral infarction. The caveat is that ipsilateral ICA disease (atheroma or dissection) is by far the most common identified cause of CRAO, whereas cardiac causes are much less common. Nevertheless, all causes of cerebral infarction have been reported to cause CRAO, and a stepwise approach that involves evaluating the most common causes first is recommended (Table 3).

What are the Indications for Conservative Therapy for CRAO?

Since the first description of CRAO by von Graefe in 1859 (77), various treatments have been advocated (Table 1). Most recommendations are based on very small series or personal experience, and none has been evaluated in a controlled clinical trial (7–27). Most ophthalmologists agree that attempting to dislodge a visible retinal embolus by ocular massage and nonaggressive decrease of intraocular pressure by medications may be useful in some patients. However, there is no evidence supporting the use of anterior chamber paracentesis, vasodilators, hemodilution, hyperbaric oxygen, or surgical removal of the embolus (8,11). Corticosteroids should only be used when arteritic CRAO (from giant cell arteritis) is suspected. Anticoagulants should be reserved for the secondary prevention of cerebral or ocular infarction in those rare patients who have an underlying disease requiring long-term anticoagulation therapy such as atrial fibrillation, acute ICA dissection, or selected hypercoagulable states such as antiphospholipid antibody syndrome.

### TABLE 3. Causes and evaluation of patients with acute central retinal artery occlusion

<table>
<thead>
<tr>
<th>Causes</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giant cell arteritis</td>
<td>CBC, platelets, ESR, CRP</td>
</tr>
<tr>
<td>Carotid disease</td>
<td>Consider fluorescein angiogram</td>
</tr>
<tr>
<td>Atheroma</td>
<td>Temporal artery biopsy if high suspicion</td>
</tr>
<tr>
<td>Dissection</td>
<td>Carotid ultrasound (with transcranial Doppler evaluating</td>
</tr>
<tr>
<td>Fibromuscular dysplasia</td>
<td>ophthalmic artery and intracranial circulation)</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>CT angiogram or MRA of head and neck</td>
</tr>
<tr>
<td>Tumor</td>
<td></td>
</tr>
<tr>
<td>Occlusion by thrombus or cardiac embolus</td>
<td></td>
</tr>
<tr>
<td>Aortic arch atheroma</td>
<td>Transthoracic ± transesophageal echocardiogram</td>
</tr>
<tr>
<td>Cardiac source of emboli</td>
<td>CT-angiogram of the aortic arch or MRA of the aortic arch</td>
</tr>
<tr>
<td>Hypercoagulable disorder</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td></td>
<td>Transthoracic ± transesophageal echocardiogram</td>
</tr>
<tr>
<td></td>
<td>Holter monitoring if indicated</td>
</tr>
<tr>
<td></td>
<td>Blood tests looking for hypercoagulable states and causes of</td>
</tr>
<tr>
<td></td>
<td>hyperviscosity, including thrombophilia, antiphospholipid antibodies,</td>
</tr>
<tr>
<td></td>
<td>hyperhomocysteinemia, sickle cell disease, mononclonal gammopathy,</td>
</tr>
<tr>
<td></td>
<td>cancer, infection, disseminated intravascular coagulation (84)</td>
</tr>
</tbody>
</table>

CBC, complete blood count; CRAO, cerebral retinal artery occlusion; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate

*This work-up is proposed as a general guideline. It needs to be adapted to the patient's age and risk factors, and clinical symptoms and signs. It also varies from one institution to another. The causes of acute CRAO and appropriate tests are organized from the most urgent or common to the least likely.
### TABLE 4. Previously published studies on the treatment of central retinal artery occlusion with intravenous thrombolysis

<table>
<thead>
<tr>
<th>Authors, year, country</th>
<th>Patients (age, range, in years)</th>
<th>Type of study</th>
<th>Conservative treatment</th>
<th>Thrombolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rossman, 1966, Germany</td>
<td>10 (39–85)</td>
<td>Retrospective</td>
<td>NA</td>
<td>IV streptokinase</td>
</tr>
<tr>
<td>Lohse and Weller, 1969, Germany</td>
<td>8 (46–74)</td>
<td>Retrospective</td>
<td>NA</td>
<td>IV streptokinase</td>
</tr>
<tr>
<td>Coscas et al, 1969, France</td>
<td>1 (45)</td>
<td>Case report</td>
<td>Retrobulbar injection of vasodilators, IV papaverine, heparin</td>
<td>IV streptokinase, corticosteroids</td>
</tr>
<tr>
<td>Sautter and Rossmann, 1971, Germany</td>
<td></td>
<td>Retrospective</td>
<td>NA</td>
<td>IV streptokinase</td>
</tr>
<tr>
<td>Guadalupi et al, 1981, Italy</td>
<td>23 (31–85)</td>
<td>Case reports</td>
<td>Hemodilution</td>
<td>IV urokinase, heparin</td>
</tr>
<tr>
<td>Annonier et al, 1988, France</td>
<td>2 (56, 43)</td>
<td>Retrospective</td>
<td>Pentoxifyllin, Aspirin</td>
<td>IV t-PA, heparin</td>
</tr>
<tr>
<td>Bertram et al, 1991, Germany</td>
<td>2 (29, 59)</td>
<td>Case reports</td>
<td>Ocular massage, AC paracentesis, rebreathing bag, SL nitroglycerin, topical medication to lower IOP</td>
<td>IV t-PA, heparin</td>
</tr>
<tr>
<td>Mames et al, 1995, USA</td>
<td>3 (56–74)</td>
<td>Retrospective</td>
<td>NA</td>
<td>IV streptokinase</td>
</tr>
<tr>
<td>Barth et al, 1996, Germany</td>
<td>2 (56, 75)</td>
<td>Retrospective</td>
<td>NA</td>
<td>IV streptokinase</td>
</tr>
<tr>
<td>Rumelt et al, 1999, Israel</td>
<td>11 (47–80)</td>
<td>Retrospective</td>
<td>Ocular massage, SL isosorbide trinitrate, IV acetazolamide, IV mannitol, 500 mg IV methylprednisolone, retrobulbar tolazoline</td>
<td>IV t-PA, heparin, aspirin</td>
</tr>
<tr>
<td>Kattah et al, 2002, USA</td>
<td>12</td>
<td>Prospective</td>
<td>Anterior chamber paracentesis if IOP &gt;12</td>
<td>IV t-PA, heparin, warfarin, urokinase</td>
</tr>
<tr>
<td>Von Mach et al, 2005, Germany</td>
<td>19 (mean age 63)</td>
<td>Retrospective</td>
<td>None</td>
<td>IV streptokinase</td>
</tr>
<tr>
<td>Yao et al, 2005, China</td>
<td>13 (38–72)</td>
<td>Retrospective</td>
<td>None</td>
<td>IV streptokinase (6 pts), IV urokinase (7 pts)</td>
</tr>
</tbody>
</table>

| In most studies, the investigators monitored the fundus and the ophthalmic artery perfusion during the infusion of thrombolysis. Thrombolysis + Studies also using intra-arterial thrombolysis. |

### How Would Thrombolysis be Performed for Acute CRAO?

In CRAO, as in cerebral infarction, thrombolytic agents can be administered intravenously or intra-arterially (into the ICA or selectively into the ophthalmic artery) (Tables 4 and 5) (1). IV thrombolysis are easy to administer even by nonspecialized physicians in the emergency room. The workup required before treatment is minimal and includes blood tests and a brain CT scan to rule out cerebral hemorrhage or a large cerebral infarction, which are contraindications to thrombolysis.

IV streptokinase was administered to a few patients with CRAO or BRAOs beginning in the late 1960s (25,29–32,35,36,45) and was subsequently replaced by urokinase (35,57,59) and t-PA (37,42,45,54), which are better tolerated (Table 4). However, IV administration of thrombolitics increases the risk of systemic as well as cerebral hemorrhage (Table 6) (28).

To decrease the risk of complications, very strict guidelines were proposed for the treatment of cerebral infarction with resultant hesitation in using such a “dangerous” treatment. Despite the success of the 1995 National
### Delay in thrombolysis

<table>
<thead>
<tr>
<th>Delay in thrombolysis</th>
<th>Results</th>
<th>Complications of fibrinolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 hours–10 days</td>
<td>1/10 pts had normal VA, 4 pts had improved VA &gt; 4 Snellen lines</td>
<td>1/11 pts had a fatal cerebral hemorrhage</td>
</tr>
<tr>
<td>5 hours–8 days</td>
<td>3/8 pts improved VA &gt; 4 Snellen lines</td>
<td>1/8 pts had a mediastinal hemorrhage</td>
</tr>
<tr>
<td>15 hours</td>
<td>Temporary improvement with VA 20/20; recurrent visual loss when streptokinase was discontinued</td>
<td>None</td>
</tr>
<tr>
<td>3 h–10 days</td>
<td>5/23 pts had improved VA &gt; 8 Snellen lines, 4/23 pts had improved VA &gt; 4 Snellen lines</td>
<td>4/23 pts with cerebral hemorrhage</td>
</tr>
<tr>
<td>4 h–7 days</td>
<td>2/2 pts had improved VA &gt; 8 Snellen lines</td>
<td>1/23 pts with shock</td>
</tr>
<tr>
<td>3–11 hours</td>
<td>4/5 pts had improved VA &gt; 4 Snellen lines</td>
<td>None</td>
</tr>
<tr>
<td>≤7 hours</td>
<td>1/2 pts had improved VA &gt; 8 Snellen lines</td>
<td>None</td>
</tr>
<tr>
<td>2.75–5.5 hours</td>
<td>2/3 had improved VA &gt; 8 Snellen lines, 1/3 pts had improved VA &gt; 4 Snellen lines</td>
<td>None</td>
</tr>
<tr>
<td>NA</td>
<td>No improvement in VA</td>
<td>2 pts had cerebral hemorrhage (1 death, 1 disabled)</td>
</tr>
<tr>
<td>1–48 hours</td>
<td>8/11 pts had improved VA &gt; 5 Snellen lines</td>
<td>None</td>
</tr>
<tr>
<td>&lt;24 hours</td>
<td>10/12 pts had improved VA, 4/10 pts had improved VA &gt; 8 Snellen lines</td>
<td>None</td>
</tr>
<tr>
<td>1–48 hours (median 5.5)</td>
<td>11/19 pts had improved VA &gt; 4 Snellen lines</td>
<td>4/19 pts with hemorrhagic complications</td>
</tr>
<tr>
<td>5–38 hours</td>
<td>IA group: 3/6 pts had improved VA by ≥4 Snellen lines; 2/6 pts had improved VA by ≥2 lines; IV group: 1/7 pts had improved VA by 2 lines</td>
<td>None</td>
</tr>
</tbody>
</table>

PO, oral; pt, patient; rt-PA, recombinant t-PA; SL, sublingual; VA, visual acuity.

was usually discontinued when reperfusion of retinal arteries or the ophthalmic artery was seen on funduscopic examination or on the angiogram.

Institute of Neurological Disorders and Stroke (NINDS) study using IV t-PA within 3 hours in acute cerebral infarction (78) and its subsequent approval by the U.S. Food and Drug Administration (FDA), the use of IV t-PA in acute stroke remains restricted because of the very short treatment window (3 hours), a widespread lack of expertise, and safety issues with a relatively high incidence of intracerebral hemorrhage and protocol violations.

The administration of IA thrombolytics directly into occluded intracranial arteries has an extended treatment window of up to 6 hours after cerebral infarction (28, 79, 80), but this use is even more limited because of reliance on the presence of an experienced interventionalist.

The same concerns and problems apply to the treatment of CRAO with IV thrombolysis. As stated earlier, IV thrombolysis is relatively easy and does not require highly specialized physicians. However, why take the risk of systemic administration of thrombolytics when only one small retinal artery is occluded? Thus, current thrombolysis for CRAO is mostly IA, requiring selective catheterization of the ipsilateral ICA and infusion of thrombolytics into the ophthalmic artery. When the ICA is occluded at
angiography, the thrombolytic agent is administered into a branch of the external carotid artery, most often the maxillary artery, the facial artery, or a meningeal artery, with the hope that the drug will reach the central retinal artery through retrograde collateral circulation. Both t-PA and urokinase are being used and doses vary (Table 5). In most cases, the IA thrombolysis is discontinued when there is clinical or angiographic evidence of revascularization of the central retinal artery. Heparin is then often given for a few days, followed by an anti-platelet agent.

Is Thrombolysis Indicated in Treatment of Acute CRAO

Case reports and studies evaluating the treatment of CRAO with IV or IA thrombolysis are detailed in Tables 4 and 5 and summarized in Table 6 (25,29–61,65). Duplication of cases was found in a few articles, and these were not included in the summary shown in Table 6 (34,38, 40,41) (only the most recently published articles by the same authors were included [35,53]). The evidence is impaired by several shortcomings.

1. There are no controlled trials. The main criticism of the previously published works on this subject is the lack of a single controlled clinical trial (51,62,63). Indeed, in all studies published to date, the visual outcome of patients with CRAO who were treated with thrombolysis has been compared to the outcome of a group of patients receiving various conservative treatments or to the presumed natural history of CRAO. Between 10% and 35% of patients with acute CRAO show visual improvement afterward, depending on how visual improvement is defined. Given that only a major improvement in vision would warrant an aggressive treatment such as thrombolysis, we have included in our summary analysis only those cases in which the authors described either “full recovery of vision” or improvement by at least 4 Snellen lines. Although some series have included patients with BRAO, we included only those with CRAO. Table 6 shows that 50 (48.5%) of 103 patients with acute CRAO treated with IV thrombolysis and 87 (34.9%) of 249 patients treated with IA thrombolysis had obvious improvement of visual acuity (at least 4 Snellen lines or “full recovery”).

These results of thrombolysis for CRAO appear to be better than those suggested in studies evaluating the natural history of CRAO or the results with other conservative treatments. Although some authors have suggested that most improvement occurs in patients treated less than 12 hours after CRAO, a correlation between improvement and treatment delay was not found in one review (51). It is difficult to perform any analysis on such a heterogeneous group of studies, and many reports do not provide enough details. Our linear regression analysis of the relationship between improvement and treatment delay showed no significant relationship.

2. There are many publication biases. It is likely that case reports and nonconsecutive small case series were only published because of relatively good outcomes and that complications of thrombolysis are under-reported (Table 6). The existing literature reports, therefore, probably overestimate the effect of thrombolysis in CRAO and underestimate the risks of using thrombolysis in patients with CRAO.

3. Thrombolysis is often performed late after the onset of CRAO. It has been suggested that the retinal tolerance time to acute ischemia is less than 240 minutes (4 hours) (81). Experimental retinal ischemia in monkeys showed that the retina can survive for approximately 100 minutes without arterial blood flow (81) and up to 3 or 4 hours when there is collateral circulation providing residual blood flow to the ischemic retina (82). The treatment window for cerebral infarction is 3 hours for IV thrombolysis (28,78) and 6 hours for IA thrombolysis (28,79,80). Although experiments evaluating the retinal tolerance time to ischemia were performed in rhesus monkeys and may not reflect exactly what is happening in humans with acute CRAO, it is likely that the treatment window does not exceed 6 to 12 hours, even in cases of incomplete CRAO when there is residual circulation (62,63,82). Therefore, there is no reason to think that revascularization procedures performed after 12 hours of retinal ischemia should have any effect on visual outcome.

Even so, thrombolitics have been administered up to 14 days after acute CRAO (Table 6) (44). Patients with up to 20 hours of visual loss are being included in the EAGLE study (IA thrombolysis is administered within 24 hours of visual loss) (65). This relatively large treatment window was chosen because retrospective reports had suggested an effect of thrombolysis even 24 hours after visual loss (49,51,53), and it was necessary to ensure recruitment of patients into the study. However, the same investigators have suggested that visual outcome is better when thrombolysis is performed within 4 hours (60), 6 hours (53,54), 7 hours (40), and 12 hours (25) after CRAO. It has also been emphasized that the visual prognosis is poor when thrombolysis is administered more than 20 hours after CRAO (41). Another factor associated with a better outcome is the severity of the CRAO (Table 2). Patients with incomplete CRAO (stages 1 and 2) probably have better collateral circulation and a longer tolerance of ischemia and may have a longer therapeutic window (4,53,66).

4. The treatment protocol has varied greatly. The main differences in treatment protocol among reported series are the route of administration and the type of thrombolytic agent used. IV streptokinase was used in early studies and has now been abandoned. Both t-PA and
urokinase (used mostly outside the United States) are now routinely used with similar results. The largest number of patients were reported by German investigators who favor IA thrombolysis (38,40,41,43,49,52,53). Selective thrombolysis into the ophthalmic artery seems a good choice to reduce the rate of cerebral and systemic hemorrhage. The dose of the thrombolytic agent is usually adjusted on the basis of revascularization of the retinal arteries evaluated on ophthalmoscopic examination (monitored during the procedure) or angiography. Table 6 emphasizes the main differences between patients treated with IV and IA thrombolysis.

The visual outcome and the complication rate has been similar in CRAO groups treated intravenously and intra-arterially, suggesting that IV thrombolysis ought still to be considered. As expected, systemic and cerebral hemorrhages were more common in the IV group, and cerebral TIAs and infarctions were more common in the group treated with IA thrombolysis. According to the authors describing these ischemic complications, the selective catheterization of the ICA and ophthalmic artery was directly responsible for distal cerebral emboli. In most of these cases, an additional dose of the thrombolytic agent was administered immediately through the same catheter into the occluded cerebral artery and many neurologic deficits resolved (and were reported as TIAs).

The EAGLE study (65) was initiated by German investigators who have the largest experience with IA thrombolysis, and their protocol involves selective catheterization of the ipsilateral ICA with infusion of the thrombolytic agent (t-PA, maximum dose of 50 mg) directly into the ophthalmic artery where possible (Table 7).

5. The outcome measures vary greatly from one study to another: Most studies have used only visual acuity to measure visual outcome. Visual fields and retinal fluorescein angiography are being performed in the EAGLE trial (Table 7) (65). However, these tests are time-consuming, and physicians are confronted with the choice of documenting the visual function and retinal appearance or treating the patient rapidly to reduce the time to treatment.

6. CRAO results from many disorders with varied prognoses: Although the cause of CRAO has not been reported in most studies, the pathogenesis of the CRAO may play a role in visual outcome and in the efficacy of thrombolysis. As emphasized by Hayreh (63,82), thrombolitics would be unlikely to provide benefit when there is a visible calcific embolus obstructing the central retinal artery. In addition, the presence of a patent cilioretinal artery probably influences visual outcome and should be noted. Finally, pretreatment evaluations rarely include imaging of the ICA other than the angiogram done during selective catheterization of the ophthalmic artery.

It has been emphasized that the most common cause of CRAO is ipsilateral carotid atheroma, and there are numerous cases described in which thrombolitics had to be administered in a branch of the external carotid artery because of ipsilateral ICA occlusion or severe stenosis. The efficiency of such a protocol in the delivery of thrombolysis to an occluded retinal artery remains unknown.

IS THE EAGLE TRIAL GOING TO PROVIDE IMPORTANT INFORMATION?

The EAGLE study is the first prospective randomized clinical trial evaluating the effect of IA t-PA compared with conservative treatment (Table 7) (65). This study should answer questions about the natural history of CRAO and the efficacy and side effects of IA thrombolysis. However, there is no true placebo arm, as patients who are not treated with thrombolysis receive some of the so-called conservative treatments, including ocular massage, therapies to lower intra-ocular pressure, aspirin, heparin, and isovolemic dilution. Although many investigators assume that “conservative treatment” is equivalent to “natural history,” it would certainly have been more powerful to compare thrombolysis to the true natural history of CRAO (82).

Subgroup analyses will be necessary for definitive interpretation of the results (based on stage of CRAO, baseline visual function, residual retinal vascularization on angiography, and mechanism of CRAO). Because the treatment window is large, there will be a need for subgroup analyses, as it is probable that most improvement will be seen among those treated early (82,83). The EAGLE study was initiated in 2002, and 16 centers from Germany, Austria, and Switzerland have been actively including patients. The investigators calculated they would need to include 200 patients (100 in each group) to reach significance. However, even in these countries where thrombolysis for CRAO is well accepted and almost routinely performed, only 47 patients had been included by April 2005 (65) and 64 patients by August 2006 (N. Feltgen, personal communication, October 2006). We will probably have to wait a few more years for the final results of this study.

IN ADVANCE OF THE REPORT OF THE EAGLE TRIAL, HOW SHOULD CRAO BE MANAGED?

There is currently not enough evidence to offer thrombolysis to all patients with acute CRAO. Caregivers have the option of enrolling patients in the EAGLE trial or in an IA treatment trial being conducted at The Johns Hopkins University under the auspices of Neil R. Miller, MD. Given the large number of published cases and the apparent relative safety and efficacy of thrombolysis in selected patients with acute CRAO, it seems reasonable to
<table>
<thead>
<tr>
<th>Authors, year, country</th>
<th>Number of patients with CRAO (age)</th>
<th>Type of study</th>
<th>Conservative treatment</th>
<th>Thrombolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annonier et al, 1984, France</td>
<td>2 pts (27, 64 y)*</td>
<td>Case report</td>
<td>None</td>
<td>IA urokinase (ICA)</td>
</tr>
<tr>
<td>Annonier et al, 1988, France</td>
<td>5 pts (25–67 y)*</td>
<td>Retrospective</td>
<td>None</td>
<td>IA urokinase (2 pts) IV urokinase (2 pts) IV streptokinase (1 pt)</td>
</tr>
<tr>
<td>Tsai et al, 1990, USA</td>
<td>1 pt (32 y)</td>
<td>Case report</td>
<td>None</td>
<td>IA urokinase (ophthalmic artery)</td>
</tr>
<tr>
<td>Schumacher et al, 1991, Germany</td>
<td>6 pts (46–77 y); 41 pts (44–87 y)</td>
<td>Retrospective</td>
<td>NA</td>
<td>IA urokinase, heparin</td>
</tr>
<tr>
<td>Mach et al, 1992, Ceskoslovakia</td>
<td>1 pt (34 y)</td>
<td>Case report</td>
<td>NA</td>
<td>IA urokinase</td>
</tr>
<tr>
<td>Schmidt et al, 1992, Germany</td>
<td>14 pts (46–87 y) received thrombolysis; 41 pts (44–87 y) received conservative treatment alone (1–12 h)</td>
<td>Prospective</td>
<td>All patients received conservative therapy; only 14 patients received thrombolysis</td>
<td>11 pts: IA urokinase; 3 pts: 30 mg IA t-PA (ICA), heparin</td>
</tr>
<tr>
<td>Schumacher et al, 1993, Germany</td>
<td>23 pts (46–87 y); 1 pt (65 y)</td>
<td>Retrospective</td>
<td>NA</td>
<td>IA urokinase IA t-PA</td>
</tr>
<tr>
<td>Valpiaus et al, 1996, Germany</td>
<td>9 pts (50–83 y)</td>
<td>Retrospective</td>
<td>IV pentoxifylline for 10 d</td>
<td>IA t-PA, heparin, aspirin</td>
</tr>
<tr>
<td>Ma et al, 1996, China</td>
<td>4 pts (&lt;70 y)</td>
<td>Retrospective</td>
<td>NA</td>
<td>IA urokinase</td>
</tr>
<tr>
<td>Weill et al, 1998, France</td>
<td>7 pts (20–82 y)</td>
<td>Retrospective</td>
<td>None</td>
<td>IA urokinase heparin, aspirin</td>
</tr>
<tr>
<td>Weber et al, 1998, Switzerland</td>
<td>17 pts (60.8 ± 15.2 y) received thrombolysis + conservative treatment vs 15 pts conservative treatment alone</td>
<td>Retrospective</td>
<td>Anterior chamber paracentesis, acetazolamide</td>
<td>IA urokinase “anticoagulation”</td>
</tr>
<tr>
<td>Wirostko et al, 1998, USA</td>
<td>1 pt (65 y)</td>
<td>Case report</td>
<td>None</td>
<td>IA urokinase, heparin</td>
</tr>
<tr>
<td>Richard et al, 1999, Germany</td>
<td>46 pts (58 ± 16 y)</td>
<td>Retrospective, systematic treatment and evaluation</td>
<td>None</td>
<td>IA t-PA, heparin</td>
</tr>
<tr>
<td>Padolecchia et al, 1999, Italy</td>
<td>3 pts (62–76 y)</td>
<td>Retrospective</td>
<td>None</td>
<td>IA t-PA</td>
</tr>
<tr>
<td>Beatty and An Eong, 2000, UK</td>
<td>Meta-analysis of 16 studies: 100 relevant pts who underwent IA thrombolysis for CRAO (19–87 y)</td>
<td>Meta-analysis</td>
<td>In some studies, patients received both conservative treatment and fibrinolysis</td>
<td>42 pts: IA urokinase 52 pts: t-PA heparin</td>
</tr>
<tr>
<td>Framme et al, 2001, Germany</td>
<td>17 pts thrombolysis (40–84 y) vs 45 pts conservative treatment</td>
<td>Retrospective</td>
<td>Decrease of IOP, improvement of rheological conditions</td>
<td>IA t-PA</td>
</tr>
</tbody>
</table>
### Delay in thrombolysis

<table>
<thead>
<tr>
<th>Delay in thrombolysis</th>
<th>Results</th>
<th>Complications of fibrinolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4 h</td>
<td>2/2 pts had mildly improved VA</td>
<td>None</td>
</tr>
<tr>
<td>3–11 h</td>
<td>4/5 pts had improved VA &gt; 4 Snellen lines</td>
<td>None</td>
</tr>
<tr>
<td>NA</td>
<td>Partial restoration of vision</td>
<td>None</td>
</tr>
<tr>
<td>5–60 h</td>
<td>All pts had improved VA; 2/6 pts recovered completely</td>
<td>1 pt with groin hematoma</td>
</tr>
<tr>
<td>6 h</td>
<td>Pt had “improved VA”</td>
<td>None</td>
</tr>
<tr>
<td>4–60 h</td>
<td>8/14 thrombolysis pts had improved VA; 3/8 thrombolysis pts had improved VA &gt; 8 Snellen lines (all were treated within 7 h after CRAO); Almost no improvement in conservatively treated pts</td>
<td>1/14 pts had a TIA</td>
</tr>
<tr>
<td>4–60 h</td>
<td>3/23 pts had full recovery; 3/23 pts had improved VA &gt; 8 Snellen lines; 2/23 pts had improved VA &gt; 4 Snellen lines</td>
<td>2/23 pts had TIAs, 1/23 pt had groin hematoma</td>
</tr>
<tr>
<td>10–37 h</td>
<td>5/9 pts had improved VA &gt; 5 Snellen lines</td>
<td>None</td>
</tr>
<tr>
<td>7–14 days</td>
<td>2/4 pts had improved VA</td>
<td>None</td>
</tr>
<tr>
<td>9–20 h</td>
<td>5/7 pts had improved VA ≥ 4 Snellen lines</td>
<td>None</td>
</tr>
<tr>
<td>&lt;6 h</td>
<td>3/17 patients had full recovery after thrombolysis; 2/17 pts had improved VA &gt; 6 Snellen lines</td>
<td>2 pts with TIA</td>
</tr>
<tr>
<td>4 h</td>
<td>Improvement from count fingers to 20/20</td>
<td>None</td>
</tr>
<tr>
<td>3–41 h</td>
<td>7/46 pts had improved VA &gt; 8 Snellen lines; 12/46 pts had improved VA ≥ 4 Snellen lines</td>
<td>2 pts with TIA</td>
</tr>
<tr>
<td>4.5–6.5 h</td>
<td>3/3 pts had improved VA; 2/3 had “complete recovery of vision”</td>
<td>None</td>
</tr>
<tr>
<td>3–60 h (mean 11.6 ± 8.7 h)</td>
<td>14/100 pts had full recovery; 27/100 pts had VA ≥ 20/40 of vision; no effect of delay in treatment on visual outcome; pts with better VA had better outcome</td>
<td>Complications in 4/100 pts: 1 pt with groin hematoma; 3 pts with minor cerebral infarctions</td>
</tr>
<tr>
<td>4–11 h</td>
<td>4/17 pts treated with thrombolysis had improved VA by &gt;2 lines; 16/45 pts treated conservatively had improved VA by &gt;2 lines</td>
<td>Complications in 3/17 pts: 1 pt with cerebral hemorrhage; 2 pts with minor cerebral infarctions</td>
</tr>
</tbody>
</table>

*Continued on next page*
TABLE 5. (Continued)

<table>
<thead>
<tr>
<th>Authors, year, country</th>
<th>Number of patients with CRAO (age)</th>
<th>Type of study</th>
<th>Conservative treatment</th>
<th>Thrombolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schmidt et al, 2002, Germany</td>
<td>62 pts thrombolysis‡ vs 116 pts conservative treatment (18–89 y)</td>
<td>Retrospective, systematic treatment and evaluation</td>
<td>Ocular massage, anterior chamber paracentesis, isovolemic hemodilution, acetazolamide, pentoxifyllin, aspirin, treatment of systemic hypertension</td>
<td>IA t-PA or urokinase anticoagulation</td>
</tr>
<tr>
<td>Fernandez et al, 2002, Spain</td>
<td>5 pts thrombolysis (47–73 y) vs 7 pts conservative treatment (57–81 y)</td>
<td>Retrospective</td>
<td>Ocular massage, anterior chamber paracentesis, acetazolamide, topical medications to decrease IOP, inhalation of O2/CO2, aspirin, retrobulbar injection of papaverine</td>
<td>IA urokinase heparin</td>
</tr>
<tr>
<td>Butz et al, 2003, Germany Switzerland</td>
<td>22 pts (40–84 y)</td>
<td>Retrospective</td>
<td>Anterior chamber paracentesis (1 pt) Hemodilution (1 pt)</td>
<td>None</td>
</tr>
<tr>
<td>Tagawa et al, 2005, Japan</td>
<td>1 pt (79 y)</td>
<td>Case report</td>
<td>None</td>
<td>IA urokinase</td>
</tr>
<tr>
<td>Yao et al, 2005, China</td>
<td>13 pts (38–72 y)</td>
<td>Retrospective</td>
<td>None</td>
<td>6 pts: IA urokinase; 7 pts: IV urokinase</td>
</tr>
<tr>
<td>Arnold et al, 2005, Switzerland</td>
<td>37 pts thrombolysis + conservative treatment (23–83 y) vs 19 pts conservative treatment alone (53–81 y)</td>
<td>Retrospective</td>
<td>Anterior chamber paracentesis, acetazolamide, heparin, aspirin</td>
<td>IA urokinase</td>
</tr>
<tr>
<td>Pettersen et al, 2005, Canada</td>
<td>8 pts (59–77 y)</td>
<td>Retrospective</td>
<td>4/9 anterior chamber paracentesis; 1/9 ocular massage Randomization between conservative treatment and thrombolysis, then heparin for 5 days for all patients</td>
<td>IA t-PA</td>
</tr>
<tr>
<td>Feltgen et al, 2006, Germany, Switzerland, Austria</td>
<td>47 pts (18–75 y)</td>
<td>Prospective randomized multicenter clinical trial</td>
<td>Ocular massage, topical medications to lower IOP, acetazolamide, aspirin, heparin, hemodilution</td>
<td>IA t-PA</td>
</tr>
</tbody>
</table>

A, artery; CRAO, central retinal artery occlusion; IA, intra-arterial; ICA, internal carotid artery; IOP, intraocular pressure; IV, intravenous; In most studies, the investigators monitored the fundus and the ophthalmic artery perfusion during the infusion of thrombolysis. Thrombolysis *The patients published by Annonier et al in 1984 (34) are also included in the article published by the same author in 1988 (35). †Studies also including patients treated with intravenous thrombolysis. ‡Some patients were reported on more than once in studies from the same German group [Schumacher et al, 1991 (38); Schmidt et al, 1992 (40); are included in the article published by Schumacher et al in 1993 (41). No details were provided in the article published by Schmidt et al in 2002 (53).
### Delay in thrombolysis

<table>
<thead>
<tr>
<th>Delay in hours</th>
<th>Results</th>
<th>Complications of fibrinolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean 10.8 ± 9.5 h</td>
<td>10/62 pts with “distinct visual improvement”; visual outcome better in Thrombolysis group; thrombolysis within 6 h of CRAO</td>
<td>Complications in 2/62 pts: 1 pt with TIA; 1 pt with cerebral infarction</td>
</tr>
<tr>
<td>11 h</td>
<td>4/5 pts treated with thrombolysis had improved VA &gt; 4 Snellen lines</td>
<td>None</td>
</tr>
<tr>
<td>4–11 h</td>
<td>9/22 pts had improved VA: 1/22 pt with normal VA (treated within 4.5 h); 6/22 pts had improved VA &gt; 8 Snellen lines; 2/22 pts had mild improvement</td>
<td>Complications in 4/22 pts: 2 pts with TIA; 1 pt with intracerebral hemorrhage; 1 pt with massive cerebral infarction</td>
</tr>
<tr>
<td>NA</td>
<td>Improvement of VA by 6 Snellen lines</td>
<td>None</td>
</tr>
<tr>
<td>5–38 h</td>
<td>IA group: 3/6 pts had improved VA by ≥ 4 Snellen lines; 2/6 pts had improved VA by ≥ 2 lines; IV group: 1/7 pts had improved VA by 2 lines</td>
<td>None</td>
</tr>
<tr>
<td>&lt;6 h</td>
<td>8/37 pts treated with thrombolysis had improved VA &gt; 20/30 (better if treated &lt;4 h after CRAO); No improvement in 19 pts treated conservatively</td>
<td>Complications in 3/37 pts: 2 pts with TIA; 1 pt with minor cerebral infarction</td>
</tr>
<tr>
<td>6–18 hrs</td>
<td>3/8 CRAO pts had improved VA by ≥ 2 Snellen lines; 3/8 pts had improved VA by 1 line; All pts with persistent VF defects (Goldmann)</td>
<td>None</td>
</tr>
<tr>
<td>&lt;20 h for inclusion (&lt;24 h for treatment)</td>
<td>Pending (study ongoing)</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA, not available; pt, patient; TIA, transient ischemic attack; VA, visual acuity; VF, visual field.

was usually discontinued when reperfusion of retinal arteries or ophthalmic artery was seen on funduscopic examination or on the angiogram.

### TABLE 6. Summary of previously reported CRAO cases treated with intravenous or intra-arterial thrombolysis

<table>
<thead>
<tr>
<th></th>
<th>Intravenous thrombolysis*</th>
<th>Intra-arterial thrombolysis†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cases</td>
<td>103</td>
<td>249</td>
</tr>
<tr>
<td>Delay of treatment after CRAO</td>
<td>1 h–10 days (mean: 16 ± 27 h, median: 6 h)</td>
<td>3 h–14 days (mean: 10.3 ± 8 h, median: 8 h)</td>
</tr>
<tr>
<td>Reported complications</td>
<td>12.6% (10 hemorrhages)</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>-2 fatal, 1 shock</td>
<td>12 TIAs,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 minor cerebral infarctions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 severe cerebral infarctions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 cerebral hemorrhages</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 groin hematomas</td>
</tr>
<tr>
<td>Improvement in visual acuity</td>
<td>48.5%</td>
<td>87/249 (34.9%)</td>
</tr>
<tr>
<td>(at least 4 Snellen lines)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improvement in visual acuity</td>
<td>34%</td>
<td>19.3%</td>
</tr>
<tr>
<td>by at least 4 Snellen lines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(but not &gt;8 Snellen lines)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Full recovery” or visual</td>
<td>14.5%</td>
<td>15.6%</td>
</tr>
<tr>
<td>acuity improved by &gt;8 Snellen lines</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Various doses of t-PA, urokinase, or streptokinase.
†Selective into the internal carotid artery, into the ophthalmic artery, or into a branch of the external carotid artery.

### TABLE 7. Summary of the European Assessment Group for Lysis in the Eye (EAGLE) Trial*

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Age 18–75 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRAO not older than 20 hours (so that the thrombolysis is administered within 24 hours of vision loss)</td>
<td></td>
</tr>
<tr>
<td>Visual acuity worse than 20/60 in the affected eye</td>
<td></td>
</tr>
<tr>
<td>Branch retinal artery occlusion</td>
<td></td>
</tr>
<tr>
<td>Cilioretinal artery supplying the macula in the affected eye</td>
<td></td>
</tr>
<tr>
<td>Serious general disease</td>
<td></td>
</tr>
<tr>
<td>“Conservative treatment” (ocular massage, lowering intraocular pressure with topical β-blocker and acetazolamide, aspirin, heparin, isovolemic hemodilution if hematocrit is &gt;40%; Intra-arterial (ophthalmic artery) thrombolysis with t-PA (maximum dose of 50 mg), followed by heparin for 5 days Visual acuity and funduscopic examinations repeated every 15 minutes by an ophthalmologist during the procedure</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Branch retinal artery occlusion</td>
<td></td>
</tr>
<tr>
<td>Cilioretinal artery supplying the macula in the affected eye</td>
<td></td>
</tr>
<tr>
<td>Serious general disease</td>
<td></td>
</tr>
<tr>
<td>“Conservative treatment” (ocular massage, lowering intraocular pressure with topical β-blocker and acetazolamide, aspirin, heparin, isovolemic hemodilution if hematocrit is &gt;40%; Intra-arterial (ophthalmic artery) thrombolysis with t-PA (maximum dose of 50 mg), followed by heparin for 5 days Visual acuity and funduscopic examinations repeated every 15 minutes by an ophthalmologist during the procedure</td>
<td></td>
</tr>
</tbody>
</table>

| Randomization of patients between two parallel treatment regimens | “Conservative treatment” (ocular massage, lowering intraocular pressure with topical β-blocker and acetazolamide, aspirin, heparin, isovolemic hemodilution if hematocrit is >40%; Intra-arterial (ophthalmic artery) thrombolysis with t-PA (maximum dose of 50 mg), followed by heparin for 5 days Visual acuity and funduscopic examinations repeated every 15 minutes by an ophthalmologist during the procedure |                 |
| Primary end point                                          | Visual acuity 1 month after therapy (compared with pretreatment visual acuity) |                 |
| Secondary end points                                      | Change in visual field (using Goldmann perimetry) |                 |
|                                                          | Effect of therapy on the retinal circulation evaluated with fluorescein angiography |                 |
|                                                          | Safety of the two treatments |                 |
|                                                          | Identification of prognostic factors (time between onset of CRAO and treatment, stage of CRAO, preexisting systemic diseases) |                 |

*Prospective, controlled, randomized study; multicenter study (16 participating centers from Germany, Switzerland, and Austria).
consider this treatment in CRAO evaluated within a few hours of onset, especially if the patient was previously functionally monocular. A survey of adults with normal vision evaluating patients’ preference for the treatment of CRAO (85) showed that 39% of surveyed adults would accept some risk of stroke and 37% would accept some risk even of death to triple the chances of recovering 20/100 visual acuity in one eye when the unaffected eye is sighted. More than 80% of persons would accept these risks if the unaffected eye is not sighted (85).

Even if the EAGLE trial confirms the efficacy of IA thrombolysis for the treatment of acute CRAO, it is hard to imagine that IA thrombolysis would become a routine treatment for CRAO. Were acute visual loss to be immediately diagnosed as CRAO and the patient referred to a highly specialized center with immediate access to the most experienced interventionalist, treatment would still probably not be administered within 6 hours after the onset of visual loss in the majority of cases. To prepare for early intervention in acute CRAO, we need to develop strategies that will allow us to evaluate all patients with acute CRAO quickly. Patient awareness and physician collaboration with emergency rooms, stroke units, and interventionalists will need to improve.

REFERENCES

48. Wirostko WJ, Pulido JS, Hendrix LE. Selective thrombolysis of
41. Schumacher M, Schmidt D, Wakhloo AK. Intra-arterial fibrinolytic
38. Schumacher M, Schmid D, Waehlo AK. Intra-arterial fibrinolysis
35. Framme C, Spiegel D, Roiser J, et al. Central retinal artery occlusion:
34. Schmidt DP, Schulte-Monting J, Schumacher M. Prognosis of central
33. Kattah JC, Wang DZ, Reddy C. Intravenous recombinant tissue-type
31. van Mach MA, Gus A, Wiedfelt J, et al. Systemic fibrinolytic therapy,
29. Beatty S, Au Eong KG. Local intra-arterial fibrinolysis for acute
27. von Mach MA, Gus A, Wiedfelt J, et al. Systemic fibrinolytic therapy,
17. van Mach MA, Gus A, Wiedfelt J, et al. Systemic fibrinolytic therapy,
11. Beatty S, Au Eong KG. Local intra-arterial fibrinolysis for acute
Joel Glaser
A Scholar’s Scholar

Jonathan D. Trobe, MD

Joel S. Glaser, MD, is widely considered one of the great scholars of neuro-ophthalmology. Educated at Duke University, the University of Miami, and the University of California, he has trained over 50 fellows. He is the author of Neuro-Ophthalmology, a highly respected and widely read single-volume textbook of neuro-ophthalmology first published in 1978 and shortly to emerge in its fourth edition. He has had a long and fruitful career at the Bascom Palmer Eye Institute, which at one time employed the largest roster of neuro-ophthalmologists ever to be assembled on one faculty. Recruited by Edward W. D. Norton, MD, then the chair of ophthalmology and himself a passionate neuro-ophthalmologist turned retina surgeon, these neuro-ophthalmologists were known as the “Miami Seven” (Lawton Smith, Noble David, Robert Daroff, Todd Troost, John McCrary, Norton, and Glaser). Having joined the Bascom Palmer faculty in 1970, Glaser is the longest running member of the Miami Seven. In collaboration now with neuro-ophthalmologist colleagues Norman Schatz and Byron Lam, Glaser is in his 37th year as a major contributor to the field.

This interview took place at his home in Coconut Grove, Florida, on December 22, 2006.

JDT: Joel, where were you born?

JSG: In Brooklyn, New York. Both of my parents were born and raised there. My father was in the practice of eye, ear, nose, and throat in Flatbush.

JDT: And your grandparents?

JSG: My mother’s parents were from Ukraine. Her name was Umansky. The little town she came from—Uman—is still there. There are, of course, no Jews there now, but it was once a great Talmudic center. My father’s parents were from Riga, Latvia—Prussian Jews. They would all have come to the United States by boat in the late 19th century. It’s a great pity that I don’t know more about

my ancestry. I had only one living grandparent when I was a child—Fanny Umansky, who lived with us. I did not record and I cannot remember much of what she told us. She loved my father. Although she kept kosher, she would cook one of his favorites—bacon—once a month. She was a great cook. Probably how I got fat...

JDT: What language was spoken at home?

JSG: English. They saved Yiddish as their code language—for when they didn’t want us kids to understand.

JDT: Were your parents religiously observant?

JSG: Not really. But my father was very knowledgeable. Later, when we were living in Orlando, Florida, the rabbi left town and, as president of the congregation, my father felt responsible to lead the Friday services—which he did! He had done a tremendous amount of reading to prepare for that. He read about two or three nonreligious books a week in addition to practicing medicine. He also played the violin and flute. I like to think that I am like him in many ways.

JDT: Where did your father train?

JSG: He went to medical school at Columbia University. He started in ENT at Columbia and then he went to the University of Pennsylvania to study with a famous bronchoscopist named Jackson.

JDT: And where did he learn ophthalmology?

JSG: Mostly self-taught. I’ve looked at his ophthalmology textbooks and, judging from the heavy underlining, I think he learned a lot of it on his own. Some he learned as a preceptor in other people’s practices.

JDT: How did the family get to Orlando?

JSG: We wound up there because my father was in the Medical Corps during the Second World War. Toward the end of the war, he was stationed at Camp Blanding in Starke, Florida, just outside Gainesville. When the war ended, my parents did not want to go back to Brooklyn. They took a tour of Florida and chose Orlando. As time went on, my father did more and more ophthalmology and less ENT.

JDT: Why?

JSG: I think he found the eye and its diseases more interesting than the nose. But one day he would do a cataract and the next day a tonsil and everyone seemed to survive. This is the life that I saw and it made me think that medicine as a career was pretty good.

JDT: What was good?

JSG: His example. He took very good care of his patients. He practiced a bit of psychology, as all good physicians must do. He was personally sensitive to his patients’ needs and genuinely enjoyed the practice of medicine. Orlando at that time was segregated. My father had one waiting room at his office. Whites and blacks could not sit in the same waiting room in Orlando in the late 1940s. My father did not understand this at first. The black patients certainly did. They would not come into the waiting room even if it was practically empty. As was customary, they sat outdoors on the hot curbside. He knew...
he could not change the system, so he built a comfortable waiting room for them off the side porch.

**JDT:** What was it like otherwise to grow up in Orlando?

**JSG:** Wonderful, ideal. This was pre-Disney. Maybe 50,000 people lived there. Every two blocks there was another lake. I eventually left in 1955, to go to college at Duke University.

**JDT:** Why Duke?

**JSG:** At the suggestion of a family friend, Joseph Weil, dean of engineering at the University of Florida. His good friend was the dean of the medical school at Duke—Wilbert Davison, brought in from Johns Hopkins University by the Duke family. Weil favored Duke Medical School. I was told that if I became a Duke undergraduate, I would have a better chance of getting into Duke Medical School. I also did not want to go where all my friends were headed, which was to the University of Florida in Gainesville.

**JDT:** To get into Duke, you must have done well in high school. Were you a scholarly guy?

**JSG:** Not really. I had a carefree life. I rode a motor scooter. I fished. I dated girls. I pitched on the baseball team. I did as much—or as little—school work as I needed to do. I got Ds in algebra. Teddy McNeil and I blew up a sink in the chemistry lab because we did not believe that elemental sodium would react vigorously with water!

**JDT:** What did you take away from the undergraduate days at Duke?

**JSG:** Half the freshman class seemed to be pre-med. I did my work. Many late nights in the library. My main outlet was fraternity life—ZBT (Zeta Beta Tau). I especially remember the annual football game that we played against the other Jewish fraternity—the TEPs. We called it the “Nose Bowl.” We played in front of at least 400 people at Wallace Wade Stadium where the Blue Devils play (or don’t play very well!).

**JDT:** Were you also involved in leadership activities?

**JSG:** I was president of the fraternity, if that’s what you mean. My main job was to explain to the Dean of Men why the gully behind the ZBT fraternity dormitory was always filled with beer bottles.

**JDT:** How about scholarly activities?

**JSG:** I majored in biology, minored in English. I remember reading the part of Lady MacBeth at the professor’s house, with Elizabethan music in the background. I took three years of French and read the original versions of Sartre, Baudelaire, and St. Exupery—the books about his experiences as a solo pilot carrying mail from the western tip of Africa to Buenos Aires, and his flying experiences during combat in World War II. These works are deeply moving. I reread them to this day.

**JDT:** And then came Duke Medical School...

**JSG:** Where every rotation was excellent. In the back of my mind was my father and the possibility of going into ophthalmic practice with him, but the rest is mostly accidents, or I should say, extraordinary luck.

**JDT:** Meaning what?

**JSG:** For my 6-week senior elective at Duke, I applied to do cardiology with Dr. Harvey Estes, but all spots were taken. I had seen a doctor named “Red Smith” (Editor: a.k.a. J. Lawton Smith, MD) cruising the wards with a cluster of ophthalmology residents in tow. He seemed to be having more fun than anyone else and luckily for me he agreed to take me on his elective for Fall 1962. In the summer of that year, I decided to go out to California to look over internships. I started in San Francisco. I had heard that ophthalmology was an excellent department, so I went by the chair’s office to get some information. While I was talking to his secretary, in came this burly bear of a man—Dr. Michael Hogan, the chair. Although suffering
from a bad cold, which made his ample nose remarkably swollen, he surprisingly and abruptly invited me into his office, knowing nothing about me. When he learned of my plans to study with Lawton Smith, he suggested I go talk to Bill Hoyt.

**JDT:** Did you know Hoyt?

**JSG:** I had never heard of him! I found him in his office at 5th and Kirkham Streets with his feet up on his desk. When I explained that I was a Duke medical student about to take an elective with Lawton Smith, he quickly pulled his legs off the desk and invited me to come spend 3 months with him after I finished with Smith. He arranged for a Fight for Sight Fellowship, which I redeemed during those 3 months by putting together plastic cut-outs of the optic nerves and chiasm. So, my career was set in motion by a substitute elective with Lawton Smith, a chance meeting with Michael Hogan, and an unplanned interview with Bill Hoyt.

**JDT:** What do you recall about your elective with Lawton Smith?

**JSG:** When I returned to Duke, I learned that Smith had accepted a position at the Bascom Palmer Eye Institute, University of Miami. Barnes Woodhall, a great neurosurgeon, was then medical school dean at Duke and, with a wide grin, gave me permission to “go and take your winter vacation with ‘Red’ Smith.” And so I followed Smith down to Florida. There I regularly had lunch with him and his close colleagues Ed Norton and Noble David. With his infectious enthusiasm, he would say that “every case is a neuro-ophth case.” I became infected, in a non-spirochetal sense. I recall especially helping to prepare teaching material for a case of acromegaly with chiasmal defects, and another patient with third nerve misdirection.

**JDT:** And what of the 3 months with Hoyt?

**JSG:** This is where I learned that it is not what you know, but when you know it. This is how it happened. We would make ward rounds on the inpatients. There was always a crowd—ophthalmologists and neurologists from Letterman General Army Hospital and from the Naval Hospital in Oakland, one or two visitors from abroad, the fellows, and, of course, the residents. Hoyt would ask a question of the group. He would go around the circle, ruthlessly prodding stomachs with an enormously long British direct ophthalmoscope. We stopped to discuss a pale middle-aged man who had visual loss in both eyes. Hoyt asked the trembling assembly: “What is the first test you would do on this man?” The dreaded ophthalmoscope pointed around like the hands of a clock, and no one seemed to come up with the right answer. Exasperated, Hoyt finally turned to the little medical student—me. Well, the patient was pale and lethargic on a neurosurgical ward, and I had just experienced pituitary tumors with Smith, so I suggested doing “a peripheral field examination.” Hoyt beamed! The youngest, least experienced member of the circle had gotten it right. And with the next patient, no one recognized third nerve misdirection but me. I was made.

**JDT:** So by the time you had finished medical school, you had already done almost 6 months of neuro-ophthalmology. A residency in ophthalmology would have seemed natural...

**JSG:** Yes, I was accepted at Bascom Palmer. They had just expanded the residency to six positions, and I am convinced I got the sixth spot. The faculty members were Norton, Smith, John Flynn, Victor Curtin, Don Gass, Bob Sexton, and Arnold Kroll. Very good teachers. They were on the ground floor and the resident clinic was on the second floor. Space was cramped, but this was good. We would simply walk the patient a short distance downstairs and say “Would you take a look?” Or the
faculty could come upstairs—and they always did. We had exposure to great ideas and great talent. And of course, there was Lawton...

**JDT:** How so?

**JSG:** His Saturday morning neuro-ophthalmology rounds were standing room only. The neurology residents usually came. Lawton had also charmed the key faculty members into attending. Always in attendance was Nobby David, an outstanding neurologist/neuro-ophthalmologist who, along with Smith, had been recruited from Duke. Even David Reynolds, the chief of neurosurgery, was there! So was Freddy Gargano, professor of neuroradiology. This was in the pre-CT (much less, MRI) era, so Freddy showed plain films, polytomes, catheter cerebral angiograms, and pneumoencephalograms.

**JDT:** Already primed, you could hardly avoid becoming a neuro-ophthalmologist...

**JSG:** Yes, and remember that Norton, the chair of ophthalmology, was himself originally a neuro-ophthalmologist. Lawton considered himself overworked, so Norton asked me if I’d consider going for a full year fellowship with Hoyt and coming back on staff.

**JDT:** And so you came to Bascom Palmer as faculty in 1970...

**JSG:** And so did Bob Daroff, who had also done a fellowship with Hoyt. As a neurologist, he was especially interested in eye movements. He was recruited by Norton and Peritz Schenberg, chair of neurology. With Daroff came Lou Dell’Osso, a nonphysician scientist, and Todd Troost, another neurologist interested in neuro-ophthalmology. At that time, there were seven card-carrying neuro-ophthalmologists at the University of Miami: Smith, Daroff, Troost, David, John McCrary, Norton, and me. (Editor: see Glaser JS. The golden age of neuro-ophthalmology at the Bascom Palmer Eye Institute. J Neuroophthalmol 2002;22:222.)

**JDT:** You came into a situation in which Lawton Smith was already ‘the king.’ Was this difficult?

**JSG:** Well, I had to politely shoulder my way in. We had different styles. People began to recognize that I was less guided by parables and rules and that I was not his assistant. My additional training with Hoyt was indispensable in these distinctions. Then along came another unexpected fortuitous event that was a major boost for my career.

**JDT:** What was that?

**JSG:** Tom Duane, then chair at Wills (Eye Hospital), was putting together his loose-leaf textbook called *Clinical Ophthalmology.* He approached Bill Hoyt, who had his hands full with Walsh’s book. Hoyt suggested that I write the neuro-ophthalmology chapters for Duane’s book, which appeared in 1976. Two years later, my chapters came out as a separate book (Editor: Glaser JS. *Neuro-ophthalmology.* Hagerstown, MD: Harper & Row; 1978). It had contributions from Daroff, Troost, and Dell’Osso.

**JDT:** What impact did the book have on your life?

**JSG:** I had to learn a lot. I wrote carefully and edited plenty. When you have to force things out in your own words, you discover how marginal some publications are. I would often say “there has to be something better than this,” and I would look again and often find nothing. I had to learn how to collect references and decide how much of the old and how much of the new material to put in. Remember that this was before computers; it was all library work. I also worked very hard on the illustrations, many of which I had done. The book is short enough so that it could become the source of basic information on common neuro-ophthalmic diseases for ophthalmology and neurology residents—and maybe even a few neurosurgery residents.

**JDT:** Haven’t you also been an editor?

**JSG:** Yes, Fred Blodi invited me onto the editorial board of the *Archives of Ophthalmology* and then I really...
had to read other people's stuff carefully. I would spend a lot of time on editorial comments and suggestions. It was educational as well as career-building. But there comes a time when family concerns take over.

JDT: As in...

JSG: I met Irena in 1977. She was secretary to Dick Forster, my colleague, and working at a desk next to my office. She was born in Czechoslovakia. Her father was actually a Czech national hero who had flown airplanes for the free Czech air force and the British Royal Air Force during the Second World War. He was shot down several times. Irena started medical studies at Charles University in Prague, but her family fled to the United States in the late 1960s when the Soviet army invaded Prague.

We were married in Miami, in 1978, and our oldest child, Larah, was born in 1982 at Hadassah Hospital in Jerusalem, where I was doing a sabbatical with Moshe Feinsod, a neurosurgeon interested in visual evoked potentials.

JDT: What of that year in Israel?

JSG: It was wonderful. The first war in Lebanon was going on. But we had a very stimulating experience living near the hospital and meeting fascinating Israeli physicians and seeing interesting patients. One of my patients was Gideon Hausner, the prosecutor of Adolph Eichmann, who was brought out of hiding in Argentina in 1961 and tried (and executed) in Jerusalem for genocide. This was when the Holocaust was "outed." Until then, survivors did not want to talk about it—either because they wanted to keep their bitter memories to themselves or because people simply didn’t believe them. Hausner’s job was to get the story out and for survivors to finally respond, “Yes, that’s right, it happened that way.”

JDT: And then you returned to Miami. What do you consider most memorable from that period?

JSG: My sons Ben and Jacob were born soon afterward. Then Irena underwent a 4-year course of study to undergo orthodox conversion. The kitchen was rebuilt kosher and we began to observe Shabbos—a big change for me, as I had grown up nonobservant. I had to give up playing tennis and watching baseball and football games on Saturdays! But every choice Irena made was correct for the family.

JDT: Do you retain your interest in Judaic studies?

JSG: Well I study less now, but I still know enough to spar with an occasional rabbi who mistakenly thinks I know more than I do. The wisdom of Jewish ethics and home life is very worthwhile. My Judaism leans less on faith and creed and more on ethical teachings. I suppose one may be an atheist and still be profoundly Jewish—many individuals are. We lost my wife Irena to stomach cancer in 1998, and I found wisdom and comfort in rabbinic writings that were directly applicable to raising three young teenage children by myself. Irena still lives in their bright eyes and generous spirits. And in my heart.

JDT: What about your publications?

JSG: In the long run, I do not think I’ve made enormous contributions to the academic literature. Maybe there are some dozen or so papers that are vaguely worthwhile. I’m thinking of my first paper: myasthenic...
pseudo-internuclear ophthalmoplegia. Nobby David, Don Gass, and Lawton Smith all made corrections, and Norton saw the last draft and evidently found no need to make any further corrections. There were the two papers in Brain, one on ischemic optic neuropathy and the other on extraocular muscle ischemia in giant cell arteritis. There were good papers on aneurysms and meningiomas of the cavernous sinus, radiation-induced optic neuropathy and chiasmopathy, and transient third nerve misdirection in migraine. Interesting case material still comes my way, but I no longer have the electricity to write it up.

**JDT:** Joel, what was your role in founding NANOS?

**JSG:** It started with the Rocky Mountain Neuro-Ophthalmology Society, which was Tom Carlow’s baby.
Treatment of Nonarteritic Anterior Ischemic Optic Neuropathy With Intravitreal Bevacizumab

Vascular endothelial growth factor (VEGF) results in a rapid and reversible increase in vascular permeability (1). Inhibition of VEGF signaling therefore provides an avenue for reducing vasogenic edema after nonarteritic ischemic optic neuropathy (NAION) and preserving viable but threatened optic nerve tissue. We report the first use of intravitreal bevacizumab (Genentech, South San Francisco, CA) for the treatment of NAION demonstrating a rapid and substantial reduction in optic nerve head edema and an unanticipated level of visual recovery.

An 84-year-old woman with a history of NAION in the right eye presented with a 3-week history of visual loss in the left eye. Visual loss was acute, painless, and nonprogressive. She denied any accompanying neurologic or ophthalmologic complaints including headaches, temporal artery tenderness, jaw claudication, or polymyalgia.

The initial ophthalmologic examination revealed optic disc swelling in the left eye with associated nerve fiber layer (NFL) hemorrhages. Sedimentation rate and C-reactive protein level were normal.

Visual acuity was 20/400 in the right eye and count fingers (CF) at 1 foot in the left eye. Confrontation visual fields demonstrated temporal islands in both eyes. Automated perimetry was not reliably performed. The pupils measured 4 mm and reacted sluggishly to light; there was a right afferent pupillary defect. The ocular ductions were full. Ophthalmoscopic examination revealed a diffusely pale, cupless right optic nerve. The left optic nerve had marked edema and peripapillary NFL hemorrhages (Fig. 1A). The neurologic examination was normal.

Optical coherence tomography (OCT) documented marked swelling of the left optic nerve (Fig. 2). Fluorescein angiography (FA) showed capillary microangiopathy and dye leakage in the mid-phase and late-phase (Fig. 3A–B). An intravitreal injection of 1.25 mg/0.05 mL bevacizumab was administered to the left eye. Nine days later, there was marked reduction in the swelling of the left optic nerve (Figs. 1B, 2) with significant resolution of the dye leakage and microangiopathy (Figs. 3C–D). The patient noticed.
concurrent improvement in visual acuity to 20/100 in the left eye.

Ten days later, visual acuity had improved to 20/70 in the left eye, and the visual field had improved (Fig. 4). Two months after injection, there remained modest inferior and superior optic disc swelling (Fig. 2). Vision has remained stable for more than 24 weeks postinjection.

After intravitreal bevacizumab, we observed a rapid and significant resolution of NAION-induced optic disc edema. Although visual recovery after NAION is not uncommon (2), the resolution of disc edema and visual recovery typically occur over 8 weeks (3). The rapid resolution of disc swelling and prompt improvement in visual acuity after bevacizumab administration suggest that VEGF-induced vascular permeability may play a role in tissue injury in NAION. Interestingly, cabergoline, a dopamine receptor agonist, inhibits VEGF-mediated vascular permeability (4). This feature may explain the potential benefit observed with carbidopa-levodopa therapy in recent-onset NAION (5).

Although local VEGF expression after NAION may promote long-term beneficial angiogenesis, acute expression may result in deleterious edema and secondary injury. Indeed, inhibition of VEGF signaling reduces cerebral edema and tissue injury in a murine stroke model (6). Therefore, VEGF inhibition may offer a novel therapeutic approach to limit injury in NAION.
A clinical trial of intravitreal bevacizumab in NAION is warranted.

Jeffrey L. Bennett, MD, PhD
Departments of Neurology and Ophthalmology
Rocky Mountain Lions Eye Institute
University of Colorado at Denver
and Health Sciences Center
Denver, Colorado
Scott Thomas, MD
Jeffrey L. Olson, MD
Naresh Mandava, MD
Department of Ophthalmology
Rocky Mountain Lions Eye Institute
University of Colorado at Denver
and Health Sciences Center
Denver, Colorado
naresh.mandava@uchsc.edu

REFERENCES
2. The Ischemic Optic Neuropathy Decompression Trial Research Group. Optic nerve decompression surgery for nonarteritic anterior ischemic optic neuropathy (NAION) is not effective and may be harmful. JAMA 1995;273:625–32.

Central Retinal Vein Occlusion as a Possible Presenting Manifestation of Sneddon Syndrome

We report a case of central retinal vein occlusion (CRVO) and livedo reticularis in a patient in whom Sneddon syndrome was subsequently diagnosed.

A 61-year-old man presented with a sudden and painless decline in visual acuity of his right eye. Visual acuities evaluated with Early Treatment Diabetic Retinopathy Study (ETDRS) measurements were 0.62 ETDRS lines (20/60 Snellen equivalent) for the right eye and 0.9 ETDRS lines (20/30 Snellen equivalent) for the left eye, there was no relative afferent pupillary defect, and intraocular pressures were 18 mm Hg in both eyes. Examination of the right fundus revealed retinal edema, optic disc swelling, tortuous and dilated retinal veins, and extensive superficial hemorrhages in all four quadrants. A diagnosis of acute CRVO was made.

Pre-fluorescein angiographic red-free fundus photography (Fig. 1) showed venous stasis but good retinal capillary perfusion, disc edema, tortuosity, and dilation of all branches of the central retinal vein and a few scattered peripheral fundus hemorrhages, consistent with nonischemic CRVO. The periphery of the eye showed no extensive areas of capillary nonperfusion or neovascularization.

The patient had no personal or family history of eye disease, systemic hypertension, diabetes mellitus, thrombophilia, or malignancy.

Systemic examination revealed a generalized livid discoloration of the skin in a net-like pattern all over the body except on the face (Fig. 2). The patient had noted the skin discoloration 13 days earlier.

Results of ultrasound studies of the heart and extracranial vessels as well as laboratory serology analyses were negative, including antinuclear antibodies (ANAs),...
FIG. 2. Left hip shows livedo reticularis, a reddish netlike discoloration of the skin.

antineutrophilic cytoplasmic antibodies (ANCAs), complement C3 and C4, antiphospholipid antibodies, and lupus anticoagulant, prothrombin time, antithrombin III, fibrinogen, protein C, protein S, and activated protein C resistance. Brain MRI showed an old cerebral infarction in the left basal ganglia. Aortic arch, neck, and brain MRA revealed no evidence of atherosclerosis or vasculitis. A skin and skeletal muscle biopsy revealed endothelial thickening in the small vessels of the subcutis without signs of vasculitis, consistent with Sneddon syndrome.

The patient was treated with 400 mg intravenous pentoxifylline daily and 7,500 IU dalteparin sodium subcutaneously for 7 days, followed by 100 mg aspirin per day.

On re-examination 3 months later, visual acuity had increased to 0.71 ETDRS lines (20/50 Snellen equivalent) for the right eye and remained at 0.9 ETDRS lines (20/30 Snellen equivalent) for the left eye. The right fundus revealed persisting optic disc swelling and retinal hemorrhages but a reduction in retinal edema. Repeated fluorescein angiography showed no signs of ischemia of the right eye.

Sneddon syndrome, first described in 1965, is characterized by generalized livedo reticularis and stroke (1,2). The etiology of this syndrome is unknown, although there are correlations with the antiphospholipid syndrome, systemic secondary vasculitis, and coagulopathies. It may start as an inflammatory and possibly immunologically mediated disorder and lead to a proliferation of smooth cells of small blood vessels and obstruction of the vessel lumen. Although central retinal artery occlusion (3–5) and peripheral retinal capillary occlusions and neovascularization (6) have been reported previously in Sneddon syndrome, CRVO has not. It is unclear whether the CRVO in our patient was directly related to Sneddon syndrome.

REFERENCES


Angiographic Shaded Surface Display Artifact Falsely Suggests Ophthalmic Artery Stenosis

We would like to alert our colleagues to an artifact commonly seen on three-dimensional reconstruction catheter angiography and CT angiograms.

We evaluated a 41-year-old healthy man with recurrent transient monocular visual loss associated with headaches and periorcular pain. He was found to have a branch retinal artery occlusion (BRAO) on ophthalmoscopic examination. Results of the initial workup with MRI and MRA, transesophageal echocardiography, and laboratory studies were unremarkable. Three-dimensional reconstruction catheter cerebral angiography demonstrated a 3 mm long right ophthalmic artery stenosis (Fig. 1A). All intracranial and extracranial large arteries, including the aortic arch, were normal.
The patient was diagnosed with isolated ophthalmic artery stenosis as the cause of recurrent visual loss and BRAO and treated with antiplatelet agents. The episodes ceased.

Isolated ophthalmic stenosis has been reported in patients with recurrent transient monocular visual loss and demonstrated mostly on digital subtraction angiography (1–3). However, further review of our patient’s angiogram demonstrated a normal-appearing ophthalmic artery on the planar digital subtraction images (Fig. 1B). The area of apparent stenosis (pseudo-stenosis) seen on the three-dimensional reconstruction images represented a shaded surface display (SSD) artifact (4). This artifact is seen relatively commonly on three-dimensional reconstruction of catheter angiograms (5) and even CT angiograms (4), suggesting that correlation of these reconstruction images with planar digital subtraction images is very important.

In our patient, this pseudo-stenosis was probably a result of a dense planum sphenoidale that projected over the proximal segment of the ophthalmic artery. Potential explanations for this artifact include thresholding errors, geometric differences in x-ray absorption for contrast material-filled structures, and incomplete filling of vessels due to hemodynamic factors (5).

Maria Woodward, MD
Department of Ophthalmology
Emory University
Atlanta, Georgia

Nancy J. Newman, MD
Departments of Ophthalmology
Neurology, and Neurological Surgery
Emory University
Atlanta, Georgia

Valérie Biousse, MD
Departments of Ophthalmology and Neurology
Emory University
Atlanta, Georgia
vbiouss@emory.edu

REFERENCES

Retinal Migraine

The central thesis of Hill et al (1) in their recent publication in this journal proposing that “definite retinal migraine, as defined by International Headache Society (IHS) criteria, is an exceedingly rare cause of transient monocular visual loss” conforms to my clinical experience. What factors can account for the persistent and unjustified inclusion of the concept of “retinal migraine” in the clinician’s diagnostic toolbox? I suggest two factors: 1) the legitimacy conferred by the IHS classification (2) and 2) the rare but incontrovertible identification of the apparently true existence of monocular migraine (3).

The most facile explanation for the perception that migraine is monocular is the frequent misperception that homonymous visual phenomena are coming from only one eye. This quandary was plainly stated in 1865 by G. B. Airy, the Astronomer Royal, who sketched and described his own migrainous fortification spectra and averred that “I have never been able to decide with certainty whether the disease really affects both eyes. The first impression on the mind is that only one eye is affected” (4).
A second explanation for the perception that migraine is monocular comes from the possibility that spreading depression (SD) is confined to the most anterior portion of the primary visual cortex, giving rise to teichopsis limited to the temporal crescent of the visual field in one eye (5). Until we have accurate functional neuroimaging during monocular migraine, SD limited to the approximately 10% of the calcarine cortex subserving the monocular temporal crescent remains plausible but unconfirmed.

Rigorous adherence to IHS criteria aids immeasurably in limiting the diagnosis of retinal migraine (IHS 1.4), but there is considerable ambiguity in descriptors of “positive visual phenomena” (criterion B). Do “scintillations” identify retinal phenomena and fortification spectra identify cortical phenomena? On the basis of Richards’ speculation in 1971 that migrainous fortifications arise from the columnar organization of visual cortex neurons specializing in “detection of lines of a particular length and orientation” (6), the “columnless” retina is judged as an unlikely site of origin for teichopsis. The distinction between the appearance of migrainous positive visual phenomena arising from cortex versus retina is blurred by reports of “simple” phosphenes heralding the cortical dysfunction of classic migraine (7).

Must we require that all retinal migraines be accompanied by headache (IHS criterion C)? The IHS concedes that “some cases without headache have been reported” (2). We should allow for the existence of “acephalgic retinal migraine” given that we allow for acephalgic migraine or “typical aura without headache” (IHS 1.2.3) in referring to painless visual disturbances of migraine.

An accurate estimate of the frequency of retinal migraine in the differential diagnosis of transient monocular visual disturbance will require more than conformation to “strict IHS criteria” (1). A revised and more precise semiology of the visual world of migraineurs is needed. For example, distinctions between the appearance (and complexity) of scintillations, photopsias, sparks, and phosphenes remain ill-defined and impede accurate classification of positive migrainous visual symptoms. Although greater precision in the description of migrainous visual phenomena will improve the nosology of migraine, accurate localization and a thorough grasp of the neurophysiology of migraine aura remain elusive.

Although Penfield and Rasmussen were unable to reproduce “zigzag outlines of migraine images” with their bipolar electrodes (8) during cortical stimulation, functional MRI mapping of blood oxygenation level–dependent (BOLD) events during migraine aura has demonstrated retinotopic progression at a characteristic SD velocity of 3.5 =/− 1.1 mm/min (9). Surprisingly, BOLD imaging in a single migraineur revealed that the initial part of the visual aura correlated with changes in the extrastriate cortex (area V3A), not in the primary visual cortex. The BOLD signal changes in migraine aura are posited to be a surrogate for SD, lending credence to Milner’s insightful theory that the scintillating scotoma corresponds to SD (10). The contemporary theory of migraine as a primarily neuronal disorder is built on the compelling consonance of functional neuroimaging, SD, and Lashley’s measurement of the “march” of his own scintillating scotoma (11). This “spreading depression theory” (12) remains ascendant despite the inability to record SD in uninjured human neocortex or retina in vivo. (1)

As neuroimaging and neurophysiologic tests for migraine evolve from the investigational stage, our contemporary clinical predicament is evocative of the approach to epilepsy before electroencephalography. Lacking a comprehensive atlas of the migraine aura, the lessons of functional neuroimaging and the solicitation of more precise descriptors of patients’ visual symptoms will go a long way toward refining the diagnosis of migraine and distinguishing retinal migraine from other monocular disturbances of vision.

Frederick E. Lepore, MD
Departments of Neurology and Ophthalmology
UMDNJ/Robert Wood Johnson Medical School
New Brunswick, New Jersey
leporefe@umdnj.edu

REFERENCES

Retinal Migraine

Based on our recently reported series of patients with retinal migraine and our literature review (1), we would like
to comment on the recent article and editorial that were published in the Journal of Neuro-Ophthalmology (2,3).

First is the editorial, “Retinal Migraine Is an Oxymoron.” The label “retinal migraine” is not a contradiction in terms any more than is the term “hemiplegic migraine.” Both conditions describe rare types of migraine defined by unusual focal symptoms.

The pathophysiology of monocular visual loss in migraine is unknown. Both spreading depression (SD) and ischemia have been proposed. Dr. Winterkorn stated that, “The pathophysiology of migraine (spreading depression of neurons) would not explain monocular visual loss.” Although the aura of migraine is usually due to SD of the occipital cortex, SD may affect neurons in any part of the brain. There is no physiological reason to assume that retinal neurons are immune to SD.

Dr. Winterkorn dismisses SD as a mechanism for retinal migraine because SD in the retina has not been reported in mammals. But it has been reported in the retinas of frogs and chicks. For almost half a century, SD of cortical neurons was dismissed as a pathophysiological mechanism of aura because it was not observed in humans.

Neurosurgeons have not seen SD in the human cortex. But the absence of evidence is not evidence of absence. Over the past decade, neuroimaging during the aura has revealed changes most consistent with SD (4).

That is not to say that vasospasm never occurs in migraine auras. It may contribute to migrainous cerebral infarction and the rare cases of retinal migraine that in time develop permanent monocular defects.

Then, in the article by Hill et al (3), the authors stated that most reported cases of retinal migraine do not meet the criteria of the International Classification of Headache Disorders (ICHD) for retinal migraine. This issue reflects problems with the diagnostic criteria. For example, Carroll (5), who introduced the term “retinal migraine,” described patients with monocular visual loss not associated with headache. Hill et al (3) found only 5 cases of definite retinal migraine and 11 others of probable or possible retinal migraine using strict ICHD-2 criteria. These criteria were based more on opinion than on a detailed review of the literature. The ICHD-2 criteria excluded cases with permanent visual loss and cases of migraine with conventional (cortical) aura. In our review (1), we included such cases.

Because most reported cases were described before publication of the ICHD-2 criteria, we used our judgment in assessing whether or not the reports of monocular visual loss were associated with “true” migraine. We were surprised that permanent visual defects were found in almost 50% of patients who had had transient monocular visual loss. The ophthalmologic examinations in these 21 patients revealed several different conditions. In some, the defects appeared to be proximal to the retina. For that reason, the term “migraine with monocular visual symptoms,” rather than “retinal migraine,” would be more appropriate. To take these factors into account, we proposed new criteria and terminology for what is now termed “retinal migraine.”

Perhaps some of the cases we cited were not truly retinal migraine. But retinal migraine may be underdiagnosed. When a patient reports blurring or blindness in one eye as the aura of migraine, we believe most doctors assume that the patient is misinterpreting a homonymous visual field defect. Doctors usually do not instruct patients to cover one eye and then the other during subsequent attacks of migraine with aura. It may turn out that retinal migraine is a frequent occurrence. That would be an oxymoron.

Seymour Solomon, MD  
Brian M. Grosberg, MD  
Department of Neurology  
Montefiore Medical Center and Albert Einstein College of Medicine  
Bronx, New York  
ssolomon@montefiore.org

Deborah I. Friedman, MD  
Departments of Ophthalmology and Neurology  
University of Rochester  
School of Medicine and Dentistry  
Rochester, New York

Richard B. Lipton, MD  
Departments of Neurology and Epidemiology and Population Health Montefiore Medical Center and Albert Einstein College of Medicine  
Bronx, New York

REFERENCES


Reply:  
We are not surprised to read that Solomon et al disagree with Dr. Winterkorn’s editorial (1) and our recently published article (2) on retinal migraine. This is a highly controversial topic, and our suggestion that “most cases labeled as retinal migraine are not migraine” has most certainly sparked a number of lively discussions.
However, none of the points raised by Solomon et al in their letter demonstrate that retinal migraine is a real entity. We do not know whether “migraine” can affect the retina or not, and our conclusion was simply that “if it does exist, retinal migraine must be exceedingly rare” (2). We also emphasized that “migraine” is by definition a benign disorder that should not result in permanent visual loss. For example, Solomon et al refer to hemiplegic migraine, a rare form of migraine still classified within the spectrum of migrainous disorders specifically because its motor deficit and confusion are always completely spontaneously reversible. We strongly disagree with Solomon et al’s statement that retinal migraine can cause permanent visual loss. Indeed, the patients included in these authors’ review (3) harbored various retinal and optic nerve disorders, including retinal artery occlusions, vein occlusions, and ischemic optic neuropathies. The wide variety of pathophysiologic conditions required to explain all these cases as retinal migraine suggests that these cases instead reflect a heterogeneous group of disorders in which there was coincidental cranial or ocular pain.

Valérie Biousse, MD
Nancy J. Newman, MD
Emory University School of Medicine
Atlanta, Georgia
vbiouss@emory.edu

REFERENCES
Adams and Victor’s Principles of Neurology, 8th Edition


Scope: This is a welcome update of the already famous neurology textbook previously written by the eminent neurologists Raymond Adams and Maurice Victor. The book is divided into 6 parts and includes 58 chapters. Like its previous edition, it is remarkably clear and practical. Whether you read it cover to cover (1,331 pages), topic by topic (6 parts), or disease by disease (58 chapters), you will gather useful information.

Strengths: After 8 editions, this book is well polished. It reads well and covers everything you may want to know in the field of clinical neurology. This very detailed textbook teaches how to think and approaches neurologic disorders by symptoms and signs and by disorders.

Weaknesses: Since its first edition was published in 1977, the text and contents have been very well updated. However, very few figures and diagrams were added and yet it remains very dense (1,331 pages packed with text in a small font). This book is not for those who need a quick answer to a question.

Recommended Audience: Neurology residents and practicing neurologists may want to own a copy of this classic textbook. It covers all aspects of general neurology and will be valuable at all levels of training.

Critical Appraisal: This is one of the classic neurology textbooks. Originally written by some of the best teachers in neurology, it has been updated by another generation of outstanding teachers.

Valérie Biousse, MD
Emory University School of Medicine
Atlanta, Georgia

Fundamentals of Neurologic Disease


Scope: This is an introductory textbook intended for medical students and beginning residents who are interested in learning the basic principles of neurology and understanding common neurologic diseases.

The beginning chapters review the basic approach to a patient with a neurologic problem, emphasizing how to use the history and neurologic examination to localize a patient’s symptoms. Key elements of the neurologic examination and a brief introduction to common neurologic tests are discussed.

Subsequent chapters are organized along the neuroaxis from muscle to cerebral cortex and emphasize the common features of groups of diseases that occur in these locations. Selected diseases that affect these areas are then discussed in more detail.

Later chapters are organized around diseases that have a common pathophysiology. Specific diseases are discussed in more depth.

Strengths: This is a concise and easy-to-read textbook that emphasizes fundamental neurologic principles and common diseases. It is well organized with clear diagrams and helpful tables. It can be read from cover to cover in a short period of time.

Weaknesses: There are minimal references. Many diseases and disease processes are left out.

Recommended Audience: Medical students, beginning residents, and practicing physicians with minimal knowledge of neurologic principles and disease processes should find this book useful.

Critical Appraisal: This is an excellent introductory textbook that will be especially useful to medical students rotating through a neurology service.

Dean M. Cestari, MD
Massachusetts Eye & Ear Infirmary
Harvard Medical School, Boston
Massachusetts

Localization in Clinical Neurology, 5th Edition


Scope: This is the fifth edition of one of the most popular books in clinical neurology. Since the first edition appeared nearly 20 years ago, this book has been within arm’s length of most neurology trainees. If localization is nearly everything in neurology—and it is—then this book has it
covered. Standard neurologic textbooks deal with localization in passing; this one moves it front and center.

The three authors, who have been in on all five editions, are all noted neurologists. Paul Brazis, a neuro-ophthalmologist at the Mayo Clinic Jacksonville, is the lead author. His coauthors are stroke experts Jose Masdeu, University of Navarra in Spain, and Jose Biller, chair of neurology at Loyola University. The fifth edition expands on previous editions largely with the addition of more schematic illustrations and references.

After an opening chapter that covers the principles of neurologic localization, each chapter is devoted to a region of the nervous system (peripheral nerves, spinal roots, spinal cord, cranial nerves, brainstem, cerebellum, hypothalamus, thalamus, basal ganglia, and cerebrum). A description of relevant anatomy is followed by a listing of the localizing features.

**Strengths:** The finesse of the authors is in highlighting and explaining the localizing features. For example, in the chapter on visual pathways, the author (undoubtedly Paul Brazis) describes the localization associated with various visual field defect patterns. In the chapter on the ocular motor system, lesions are associated with each segment of the third, fourth, and sixth cranial nerves. Remarks are amply supported by references—trustworthy and up-to-date. The more difficult issues are illustrated with schematic diagrams.

**Weaknesses:** When material is organized and presented according to location of the lesion, the reading gets a bit dry. It is rather like learning a language entirely by studying grammatical rules. The reference lists are still loaded with some of the citations from the original editions, which are now out of date and not as valuable. The description of very rare causes sometimes clogs the text.

**Recommended Audience:** This book will be useful to anyone who deals with neurologic disease and especially to neuro-ophthalmologists with casual training in neurology.

**Critical Appraisal:** When they launched the first edition of this book more than 20 years ago, the authors were on something in recognizing that the fundamental quest in neurology is to localize the lesion. With keen scholarship, they have pulled together the relevant information from their extensive experience in examining patients and in reading the neurologic literature. It is no surprise that trainees in neurology have embraced each edition. Coverage is broad and diagnostic nuggets are plentiful. This fifth edition is even better than the fourth.

Jonathan D. Trobe, MD
University of Michigan
Ann Arbor, Michigan

---

**Cranial Nerves: Functional Anatomy**


**Scope:** This is a pocket-sized compilation of anatomic, functional, and clinical notes on the cranial nerves written by a senior anatomist.

The book’s 140 small pages are separated into an introductory section surveying overall cranial nerve organization and anatomic and functional basics such as nuclei, ganglia, and brainstem organization and then 5 sections divided by function: 1) chewing and facial sensation; 2) pharynx and larynx, swallowing, and phonation; 3) autonomic components, taste, and smell; 4) vision and eye movements; and 5) hearing and balance. In each chapter, the main anatomic features of each nerve are followed by a few common clinical “pearls” and a few details of clinical testing. Some tables are provided, especially in the introductory portion, as are many simple line drawings throughout the remainder of the text.

As indicated in the author’s acknowledgments, this book grew from notes written in the process of teaching medical and dental students. The notes were first published in a condensed form in the author’s previously published clinical anatomy textbook.

Unlike previous approaches to this subject, this book does not approach the cranial nerves in order by number, nor does it approach them in a purely embryologic or evolutionary fashion. Instead, it considers the cranial nerves in functional units, “encountering them much as would an ingested morsel of food.” Simple clinical relevance is added to “lend spice” to the process.

**Strengths:** The book is short, portable, and to the point. The line diagrams are clear.

**Weaknesses:** Simplification, generalization, and even a few inaccuracies are inevitable in a book of this size and scope, especially as regards the clinical notes and the methodologies of testing the cranial nerves.

**Recommended Audience:** This book was written for students of medicine, dentistry, and speech therapy, but it could be useful for practicing physicians, dentists, and other health care providers involved in the clinical examination of the head and neck. It is not meant to replace textbooks and basic courses of functional anatomy but rather is meant to be a quick reminder.

**Critical Appraisal:** This is a worthwhile guide to the functional anatomy of the cranial nerves approached in an unorthodox fashion by a seasoned anatomist and teacher who never loses sight of clinical relevance.
Clinical Neuropathology: Text and Color Atlas


Scope: This is a 324-page textbook and atlas that covers principles and major categories of neuropathologic disease. It is meant to occupy a spot this side of Greenfield’s Neuropathology, a massive two-volume work.

Strengths: Authored by a physician certified in pathology and clinical neurology, the book is extremely well-written and concise. It incorporates up-to-date pathogenetic thinking based on recent developments in molecular biology. The illustrations are plentiful, beautiful, and easily decoded with well-crafted legends.

Weaknesses: Some topics are given little or no attention, a trade-off that the reader readily accepts in return for a highly accessible source.

Recommended Audience: Medical students and clinicians who deal with aspects of the nervous system should find this textbook useful.

Critical Appraisal: This book is an eminently readable source in a field that is unapproachable for most clinicians. I found that I was able to read it from cover to cover without much effort. The text and photographs jibe wonderfully. Neuropathology may not come alive, but at least it’s out there. A good book like this, with its well-executed simplification, brings insights that penetrate.

Jonathan D. Trobe, MD
University of Michigan
Ann Arbor, Michigan

Neurology and Trauma, 2nd Edition


Scope: This is a comprehensive multi-authored textbook dealing with the neurologic consequences of traumatic injury to the central and peripheral nervous systems. It is the second edition of a book originally published in 1996. An additional 20 chapters have been added with new sections on neurologic sports trauma and iatrogenic trauma.

The book is divided into 7 sections. The first 3 are the long-established topics in neuro-trauma: head trauma, spinal trauma, and peripheral nerve injuries. In addition to the epidemiology, history, radiographic evaluation, and management of traumatic brain injury, spinal cord injury, and peripheral nerve injuries, Dr. Evans addresses topics such as posttraumatic epilepsy, complications of spinal cord injury, and evaluation of the brachial plexus. The final three chapters in the head trauma section offer unique perspectives with regard to the neurobehavioral and neuropsychologic implications of traumatic brain injury and place them in the framework of capacity for rehabilitation.

The final 4 sections address neuro-trauma in the context of specific scenarios: posttraumatic pain syndromes, sports and neurologic trauma, environmental trauma, posttraumatic conditions, medicolegal aspects, and iatrogenic trauma.

Strengths: This book reaches far beyond the traditional topics and delves into subjects rarely addressed in neuro-trauma textbooks. Posttraumatic pain syndromes, sports and neurologic trauma, and posttraumatic conditions are wonderfully reviewed to provide valuable information for the clinician who examines victims of trauma in the acute setting and long after injury.

Weaknesses: The only deficiency is the limited review of spinal cord injury. The basic science and recent clinical research on this topic are sparse. By comparison, these subjects are exhaustively reviewed for traumatic brain injury. Although such detail may be beyond the scope of the author’s intent, further discussion regarding the successes and failures of recent clinical trials, as well as the science behind them, would complement the equivalent data presented on traumatic brain injury and give perspective on the topic of future research on spinal cord injury.

Recommended Audience: This book will be a valuable resource for neurosurgeons, neurologists, trauma surgeons, emergency department physicians, physiatrists and all physicians who treat victims of trauma in the acute or chronic setting.

Critical Appraisal: The author has masterfully edited a comprehensive text on the neurologic implications of trauma. This multi-authored textbook remains remarkably cohesive throughout. From the basic science and recent clinical research to the acute clinical scenarios and chronic outpatient issues, this text will be of value to those physicians who interact with patients who have endured trauma to the central or peripheral nervous system.

Luis M. Tumialán, MD
Department of Neurosurgery
Emory University School of Medicine
Atlanta, Georgia
Digital Neuroanatomy: An Interactive CD Atlas With Text


Scope: This interactive CD and its accompanying text cover introductory level microscopic and gross neuroanatomy. The CD and book are organized into 6 chapters: light microscopy; electron microscopy; skull, meninges, and spinal cord; gross brain anatomy; sectional brain anatomy; and an introduction to neuroimaging.

Strengths: The CD is fantastic. It contains interactive study and quiz modes. In study mode, there are excellent quality images accompanied by illustrative text. These images are labeled only by letters that, when pressed, reveal the name of the structure—an ideal way to study. The quizzes contain hundreds of multiple choice questions to evaluate one's mastery of the material. The introduction to neuroimaging contains normal and abnormal images.

Weaknesses: The brief book follows the same general organization as the CD and generally contains information already found on the CD. When this is not the case, it seems that the text could have been easily included on the CD. The only true loss one would incur from tossing the book would be the line drawings that illuminate the three-dimensional organization of micrographs and pathology sections. These drawings should have been a part of the CD. The CD unfortunately only runs on Windows. Another minor weakness is that the neuroimages are sometimes presented sideways, which requires some mental exercise in interpretation.

Recommended Audience: This book is appropriate for graduate and first-year medical students taking a neuroanatomy course. Teachers of neuroanatomy may find this to be a useful resource and question bank.

Critical Appraisal: This textbook with the CD would be an excellent accompaniment and study tool for an introductory course in neuroanatomy.

Beau B. Bruce, MD
Emory University School of Medicine
Atlanta, Georgia
Upcoming Meetings

Sept. 10–Sept. 12, 2007
30th Annual Meeting of the Japan Neuroscience Society
Yokohama, Japan
http://www2.convention.jp/neuro2007/index.html
Contact: neuro2007@convention.jp

Sept. 15–Sept. 20, 2007
Congress of Neurological Surgeons 57th Annual Meeting
San Diego, CA
Contact: info@lcons.org

27th Pupil Colloquium
Hamamatsu City, Japan
Contact: pupil27@kitasato-u.ac.jp

Oct. 3–Oct. 6, 2007
European Association for Vision and Research (EVER)
Portoroz, Slovenia
Contact: ever@ever.be

132nd Annual Meeting of the American Neurological Association
Washington, DC
http://www.aneuroa.org
Contact: julieratzloff@llmsi.com

Nov. 3–Nov. 7, 2007
37th Annual Meeting of the Society for Neuroscience
San Diego, CA
http://www.sfn.org/am2007/
Contact: info@sfn.org

Nov. 10–Nov. 13, 2007
Annual Meeting of the American Academy of Ophthalmology (AAO)
New Orleans, LA
http://www.aao.org/annual_meeting/2007.cfm
Contact: meetings@aaos.org

Nov. 30–Dec. 1, 2007
45th Annual Meeting of the Japanese Neuro-Ophthalmology Society (JNOS)
Osaka, Japan
http://www.senri-ic.co.jp/ [Japanese only]
Contact: Tomiko Matumoto, MD, phone: +81-72-299-1122

31st Annual Meeting of the American Society of Neuroimaging
Tucson, AZ
http://asnweb.org
Contact: asa@llmsi.com

Feb. 20–Feb. 22, 2008
International Stroke Conference
New Orleans, LA
http://strokeconference.americanheart.org/portal/strokeconference/ac/
Contact: strokeconference@heart.org

March 8–March 13, 2008
34th North American Neuro-Ophthalmology Society (NANOS) Annual Meeting
Orlando, FL
http://www.nanosweb.org/meetings/index.htm
Contact: info@nanosnet.org

April 2–April 6, 2008
American Association of Pediatric Ophthalmology & Strabismus (AAPOS) Annual Meeting
Washington, DC
http://www.aapos.org
Contact: aapos@aaos.org

April 12–April 19, 2008
60th Annual Meeting of the American Academy of Neurology (AAN)
Chicago, IL
http://am.aan.com/
Contact: membership@aan.com

April 26–May 1, 2008
76th American Association of Neurological Surgeons (AANS) Annual Meeting
Chicago, IL
Contact: info@aans.org

April 27–May 1, 2008
Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting
Ft. Lauderdale, FL
http://www.arvo.org
Contact: arvo@arvo.org
May 13–May 16, 2008
European Stroke Conference
Nice, France
http://www.eurostroke.org/esc_congresses.htm
Contact: hennerici@eurostroke.eu

May 16–May 18, 2008
4th Asian Neuro-Ophthalmology Society Meeting
Taipei, Taiwan
Contact: asnos2008@yahoo.com.tw

May 18–May 20, 2008
Society of Neurological Surgeons Annual Meeting
Madison, WI
http://www.societyns.org/meeting/index.html

May 21–May 24, 2008
18th International Visual Field and Imaging Symposium
(International Perimetric Society)
Nara City, Japan
http://www.congre.co.jp/ips2008/
Contact: ips2008@congre.co.jp

June 1–June 5, 2008
46th Annual Meeting of the American Society of Neuroradiology (ASNR)
New Orleans, LA
Contact: meetings@asnr.org

June 7–June 11, 2008
18th Meeting of the European Neurological Society
Nice, France
http://www.akm.ch/ens2008
Contact: ensinfo@akm.ch

June 7–June 12, 2008
International Neuro-Ophthalmology Society (INOS)
Napa, CA
Contact: info@inos2008.org

June 11–June 14, 2008
Canadian Ophthalmological Society Annual Meeting
Whistler, BC, Canada
http://www.eyesite.ca/english/calendar.htm
Contact: kross@eyesite.ca

June 24–June 27, 2008
XIX Symposium of the International Society on Metabolic Eye Disease
Guangzhou, China
Contact: optoedcorp@aol.com

June 26–June 29, 2008
50th Annual Scientific Meeting of the American Headache Society
Boston, MA
http://www.americanheadachesociety.org
Contact: ahsmtgs@talley.com

June 28–July 2, 2008
World Ophthalmology Congress
XXXI International Congress of Ophthalmology
XII Chinese Ophthalmology Symposium
XX Hong Kong Ophthalmological Symposium
Hong Kong, China
http://www.woc2008hongkong.org/
Contact: info@woc2008hongkong.org

July 9–July 11, 2008
31st Annual Meeting of the Japanese Neuroscience Society
Tokyo, Japan
Contact: neurosci2008@congre.co.jp

July 12–July 16, 2008
6th Forum of European Neuroscience Societies (FENS)
Geneva, Switzerland
http://fens2008.neurosciences.asso.fr/
Contact: gibson@mdc-berlin.de

Aug. 23–Aug. 26, 2008
12th Congress of the European Federation of Neurological Societies (EFNS)
Madrid, Spain
http://efns2008.efns.org/
Contact: efns08@kenes.com

Sept. 21–Sept. 26, 2008
XVIII International Congress of Eye Research (ICER)
Beijing, China
Contact: mail@iser.org

Sept. 24–Sept. 27, 2008
6th World Stroke Congress
Vienna, Austria
http://www.kenes.com/stroke2008/
Contact: stroke2008@kenes.com