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Journal of Neuro-Ophthalmology (ISSN: #1070-8023). Is published quarterly in March, June, September, and December by Lippincott Williams & Wilkins, at 16522 Hunters Green Parkway, Hagerstown, MD 21740-2146. Business and production offices are located at Two Commerce Square, 2001 Market Street, Philadelphia, PA 19103. Periodicals postage paid at Hagerstown, MD and at additional mailing offices. Copyright © 2013 by North American Neuro-Ophthalmology Society.

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Annual Subscription Rates: United States—$526.00 Individual, $1,048.00 Institution, $207.00 In-training. Single copy rate $283.00. All prices include a handling charge. Subscriptions outside the US must add $11.00 for airmail delivery. United States residents of AL, CO, DC, FL, GA, HI, IA ID, IN KS, KY, LA, MD, MO, ND, NM, NV, OR, SC, SD, UT, VT, WA, WV and state sales tax. The GST tax of 7% must be added to all orders shipped to Canada (Lippincott Williams & Wilkins' GST identification #985524259). Subscriptions sent by airfreight to outside the United States must be prepaid. Prices subject to change without notice. Visit us online at www.jneuro-ophthalmology.com.

POSTMASTER: Send address changes to Journal of Neuro-Ophthalmology, P.O. Box 1550, Hagerstown, MD 21740

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United States Health Care Reform:
Neuro-Ophthalmologist, W(h)ither Thou Goest?

Howard R. Krauss, MD, Susan M. Pepin, MD

According to baseball legend Yogi Berra, “The future ain’t what it used to be.” This is exemplified by the tectonic shifts occurring today in the US health care landscape. Although it’s easy to understand the consequences of the subduction of the Pacific Plate by the North American Plate, the results of the tectonic plate shifts in US health care are harder to comprehend. Perhaps neuro-ophthalmologists are impotent in their abilities to prevent earthquakes, tsunamis, or volcanic eruptions but that does not negate the value of anticipation, preparation, and adaptation; and perhaps, when it comes to health care reform, it is not yet too late to establish and retain a rightful position of importance for neuro-ophthalmology. If so, our value is not likely to be adequately acknowledged by simply continuing our excellent job of research, teaching, and patient care; we have to lift our heads up, individually and collectively, wake up, turn on the lights, get up, and get involved in health care reform.

The earth has 7 primary tectonic plates and many secondary and tertiary plates. Forces governing the movements of these plates include gravity, drag, convection, suction, forces generated by the rotation of the globe, and tidal forces generated by the sun and the moon.

The tectonic plates of the US health care can be similarly categorized. Primary plates include Center for Medicare and Medicaid Services (CMS), state, and county health care programs; employer-sponsored health insurance/health plan industry; the pharmaceutical industry, the technology/implant/equipment industry; and hospitals. The secondary and tertiary plates include physicians, allied health professionals, patients, ambulatory surgical centers, imaging centers, and diagnostic laboratories. Forces governing the movements of these plates include societal needs and well-being, disease burden, cost, funding, laws, regulations, judicial decisions, political campaign contributions, lobbying expenditures, empathy, compassion, generosity, inertia, fear, and greed.

The ground has been shifting and heaving for billions of years. We have all seen suspenseful sci-fi films where something triggers rapid shifts of the tectonic plates, and we witness the torturous deaths of billions while we root for a few survivors. Similarly, the tectonic plates of health care in the United States have been shifting for at least a hundred years. In 1912, Theodore Roosevelt brought the progressive proposal for universal health care into his Bull Moose Party campaign against incumbent Republican William Howard Taft and Democratic candidate Woodrow Wilson. From 1933 to 1935, Franklin Roosevelt attempted to fold publicly funded health care into Social Security legislation. Harry Truman called for universal health care as a part of his Fair Deal in 1949. The Medicare program was established by legislation signed into law on July 30, 1965, by Lyndon Johnson.

The 2010 Patient Protection Affordable Care Act (PPACA or Obamacare) is creating rapid shift, with uncertainty and anxiety between patients and doctors. We are left hoping that we may be among the survivors. PPACA has been a veritable political football, and although the effects of federal health care reform are still yet to be fully implemented, our landscape is one of the shifting payment paradigms, medical group, hospital and health plan mergers and acquisitions, ever-changing state legislation and regulation, and ever-increasing costs. In Los Angeles County, the Medical Association remains in a battle with the state over its plans to shift 450,000 Medi–Medi patients into HMOs this year. Consequences may include serious jeopardy to the lives and well being of thousands of patients and financial failure of hundreds of practices, which have cared for these patients. In California, where the state health insurance exchange was ahead of the curve, online and functional on October 1, 2013,
Many patients have lost their well-being above your personal plan of action today. Become proactive in the changing paradigm of US health care or be prepared to be swept aside!

We are the Rodney Dangerfields of US health care. Neuro-ophthalmologists have survived as residency program directors, ophthalmic surgeons, electromyographers or oculoplastic, strabismus, or LASIK surgeons, who dabble in neuro-ophthalmology. Ironically, the value of clinical neuro-ophthalmology is a too closely guarded secret; so much so that we seem to be undervalued. What is the value of listening to a patient? What is the value of asking clinically appropriate questions, rather than a standardized 15-point history and review of systems? What is the value of diagnosing a patient with Horner syndrome? What is the value of detecting a carotid dissection before a stroke? What is the value of detecting an aneurysm before a subarachnoid hemorrhage? What is the value of detecting hyperthyroidism before cardiac failure? What is the value of preventing blindness? The list of our valuable life-saving and morbidity-sparing interventions is nearly endless. Obviously, neither we, nor the business managers, nor the department chairs, nor the Deans, nor the for-profit insurance industry executives, nor the hospital administrators, nor the CMS have a full understanding of the value of clinical neuro-ophthalmology. We must individually and collectively recognize our value and commit ourselves to assuring that our value in the US health care system is understood. We must be transparent in our costs, we must quantify our value, we must collect and publish data. This is a project for NANOS: “A Cost/Benefit and Outcomes Analysis of Neuro-ophthalmic Evaluation and Management.”

And what can we do individually? 1) Do not despair; continue to be an ethical and compassionate physician; 2) Continue your dedication to research, teaching, and patient care; 3) Continue to hold your patients’ well-being above your own personal interest and serve as your patients’ advocate; 4) Hold your patients responsible for partnering in their well being and let them know that as insurance subscribers and voters, you are depending on them to advocate for maintenance of access to neuro-ophthalmologists; 5) Be active in educating your medical and general community about what you do; and 6) Get involved in your local, state and, if possible, national medical and political communities.

Most importantly, our patients and patients-to-be need us to stand up for them now and for their future. Begin your personal plan of action today. Become proactive in the changing paradigm of US health care or be prepared to be swept aside!
The Idiopathic Intracranial Hypertension Treatment Trial: Design Considerations and Methods

Deborah I. Friedman, MD, MPH, Michael P. McDermott, PhD, Karl Kieburtz, MD, MPH, Mark Kupersmith, MD, Ann Stoutenburgh, CCRC, John L. Keltner, MD, Steven E. Feldon, MD, MBA, Eleanor Schron, PhD, RN, James J. Corbett, MD, Michael Wall, MD; for the NORDIC IIHTT Study Group

Background: The objectives of this study were to present the rationale for the main aspects of the study design and describe the trial methodology for the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT).

Methods: Eligible candidates with mild visual field loss (automated perimetric mean deviation [PMD] −2 to −7 dB) were randomized to receive either acetazolamide or matching placebo tablets. Randomized participants were offered participation in a supervised dietary program. The primary outcome variable, PMD, was measured at 6 months. Additionally, cerebrospinal fluid from subjects and serum from study participants and matched controls were collected for genetic analysis and vitamin A studies. An ancillary optical coherence substudy was added to investigate the changes of papilledema in the optic nerve head and retina that correlate with Frisén grading, visual field deficits, and low-contrast visual acuity.

Results: The randomized trial entered 165 participants from March 17, 2010, through November 27, 2012, from the United States and Canada. The primary outcome (month 6) visits were successfully completed by June 15, 2013. Blood specimens were obtained from 165 controls without IIH to investigate vitamin A metabolism and genetic markers of potential risk factors for IIH.

Conclusions: The IIHTT is the first randomized, double-masked placebo-controlled trial to study the effectiveness of medical treatment for patients with IIH.

doi: 10.1097/WNO.0000000000000114

Idiopathic intracranial hypertension (IIH), also called pseudotumor cerebri, is a disorder of elevated intracranial pressure of unknown cause (1). Its yearly incidence is 22.5 per 100,000 in overweight women of childbearing age and is rising in parallel with the obesity epidemic (2,3). It affects about 100,000 Americans. Most patients suffer debilitating headaches. Because of pressure on the optic nerve (papilledema), 86% have some degree of permanent visual loss and 10% develop severe visual loss (4). Although a number of interventions have been used in clinical practice to prevent loss of sight, none has been proven effective. The most recent Cochrane review stated, “There is insufficient information to generate an evidence-based management strategy for idiopathic intracranial hypertension. Of the various treatments available, there is inadequate information regarding which are truly beneficial and which are potentially harmful. Properly designed and executed trials are needed” (5).

No randomized clinical trial in patients with visual loss from IIH had been performed before the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) for several reasons. IIH is officially classified as a “rare disease” by the National Institutes of Health (www.rarediseases.info.nih.gov), raising concern over the feasibility of recruiting a sufficiently large sample of participants. A wide variety

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of treatments are used in clinical practice, including dietary interventions, carbonic anhydrase inhibitors, diuretics, cerebrospinal fluid diversion procedures (shunts), and optic nerve sheath fenestration (ONSF). The indications for various treatments are not well defined, and there has been considerable controversy regarding the threshold for using surgical therapy, as well as which surgical therapy is preferable to study. No prospective studies have shown a specific therapy to control or improve IIH symptoms and signs or to consistently prevent or reverse vision deterioration. Nonetheless, many neuro-ophthalmologists were uncomfortable incorporating a placebo group in a treatment trial of IIH, believing that some type of active treatment was necessary despite the lack of evidence. Thus, although experts in the field convened annually to discuss the possibility of a trial for almost 20 years, they were unable to concur on the intervention to be studied, and the subpopulation of patients to include, the nature of the control group, and the outcome variables to be assessed.

With the epidemic increase in obesity in the United States, Canada, and many countries outside of North America, the incidence of IIH is expected to continue rising (4). The morbidity and health issues associated with IIH have a socioeconomic impact on the affected individual as well as the health care system. Because of resulting disability from debilitating headaches and vision loss and the limited scientific rationale to guide treatment decisions, the National Eye Institute determined that critically evaluating the cause, ti

Study Objectives

The IIHTT was a multicenter, randomized, double-masked placebo-controlled trial to determine the efficacy of acetazolamide (up to 4 g/d) compared with placebo, with everyone receiving intervention with a supervised weight-reduction program, in reducing or reversing visual loss after 6 months of intervention (Fig. 1). The study population were individuals with IIH and mild visual field loss (initially baseline perimetric mean deviation [PMD] of $-2$ to $-5$ dB, later expanded to include PMD up to $-7$ dB, in the most affected eye). The primary outcome variable of PMD in the most affected eye (study eye) at randomization was analyzed at 6 months. Randomized participants were followed up to 12 months and yearly thereafter. Additional objectives included determining associations between the study interventions and visual field defects, Frisén papilledema grade, and the severity and frequency of headaches.

Study Population

Preliminary Data and Rationale for Recruitment Potential

In anticipation of potentially needing 200 or more participants for a treatment trial, an initial survey was done by the IIH Study Group in 2000 to determine the numbers of patients with IIH seen in 18 Neuro-ophthalmology
centers. Patients aged 18–60 years meeting the modified Dandy criteria (6) for IIH were included in the survey. De-identified data were collected from 380 patients (35 men and 345 women) seen in a 1-year period from June 1999 through June 2000. Treatments used included acetazolamide, furosemide, or other diuretics (71%), a weight reduction diet alone (19%), lumbarperitoneal shunt (12%), ONSF (12%), corticosteroids (3%), and repeated LP (1%), and 4% received no treatment. Some patients were treated with multiple interventions. These data documented that IIH is encountered frequently enough in a Neuro-ophthalmology practice to support adequate recruitment, that management regimens vary considerably and that acetazolamide and other diuretics were the most frequently used treatments.

IIH Randomized Participants
The inclusion and exclusion criteria are listed in Table 1. Adolescents were not included because previous experience by the New York Obesity Nutrition Research Center (NYONRC) found that children in this age group had difficulty adhering to a dietary protocol, which was a required co-intervention in this study. Use of topiramate, corticosteroids, and other diuretics was not permitted during the double-masked phase of the trial.

Human Subjects Protection and Regulatory Approvals
The IIHTT protocol was approved by the Research Subjects Review Board at the University of Rochester and the Institutional Review Boards (IRBs) at the University of Iowa and St. Luke’s Roosevelt Hospital before being sent out to the study sites. The study was approved by IRBs at all sites, and at sites without a governing IRB, by Western IRB. All treatment trial participants and control subjects provided written informed consent. The IIHTT was registered on clinicaltrials.gov.

As acetazolamide is not approved by the Food and Drug Administration (FDA) for the treatment of IIH, an investigational new drug (IND) application was submitted. The FDA and Health Canada waived the need for an IND for the IIHTT.

Outcomes for Treatment Intervention
Primary Outcome Variable: Perimetric Mean Deviation
Rationale
We used PMD on the Automated Visual Field Analyzer as a global measure of visual function and as an outcome. We chose PMD because of its more stable retest variability compared with individual or groups of test locations and its sensitivity to global clinically meaningful changes in IIH (7). Papilledema grade was considered but not used as a primary outcome variable because “improvement” may also occur as optic atrophy develops. To further define the range of PMD acceptable for inclusion, the IIHTT Steering Committee members performed a retrospective chart review of 154 consecutive patients who met the modified Dandy criteria for IIH from 5 Neuro-ophthalmology centers. All patients had follow-up visits within 4–12 months with manual or automated perimetry. Data were abstracted from 109 eligible patient charts.

The presenting PMD ranged from $-35$ to $+1.29$ dB with a median of $-3.11$ dB. Of the 109 patients, 14 had no visual loss and 48 had mild visual loss (PMD: $-2$ to $-5$ dB). Thirty-seven patients had a PMD of $-2$ dB or worse but better than $-5$ dB. There were 26 patients with moderate visual loss, defined as PMD $-5$ dB to $-14$ dB, and 13 patients had a PMD worse than $-14$ dB. In patients with mild visual loss, the mean ± standard deviation (SD) change in PMD in the worst affected eye over 6.4 ± 1.9 months of observation was $0.82 ± 2.35$ dB. These data were used to plan the sample size for the IIHTT.

The initial visual metric for study eligibility was a PMD from $-2$ to $-5$ dB as most neuro-ophthalmologists treat this range of visual loss medically in practice. Patients with a PMD better than $-2$ dB at baseline were excluded because a normal PMD precluded the ability to assess significant improvement over time. During the course of the study, the visual field eligibility metric was expanded to include cases with a PMD up to $-7$ dB to facilitate recruitment.

IIHTT Visual Field Procedure
Automated perimetry was performed using the SITA Standard program 24-2 in both eyes. The testing was performed by a technician certified by the Visual Field Reading Center (VFRC) using the IIHTT manual of procedures for the VFRC. Each candidate had at least 2 initial visual field examinations done at least 1 hour apart. As the primary outcome variable was change in PMD from baseline to month 6 in the eye with the worse PMD at baseline, potential enrollees were required to provide reliable and reproducible visual field examinations (i.e., able to maintain fixation using an eye monitoring device, <15% false-positive errors) at the screening visit to be eligible for participation.

Because the LP can transiently lower intracranial pressure and potentially improve visual function, the study used the following protocol: the baseline PMD was the average of the PMD from 2 qualifying visual fields. If the patient had an LP done more than 1 week before the screening visit, qualifying perimetric testing was performed during the first visit. If the LP had not yet been performed, a single perimetric test was done on each eye before the LP. The second test for each eye was done after the LP. If the VFRC determined that the initial 2 visual field results agreed and met VFRC reliability standards, regardless of the timing of the LP, these visual fields served as the qualifying baseline visual fields. If they did not agree, a third visual field was performed on the study eye. If the visual field was reliable, the third field served as one of the 2 qualifying baseline fields, but if it was unreliable, another visual field was performed.
The vision in the eye with the most perimetric visual loss based on PMD was considered the study eye for the purposes of the primary outcome assessment, but both eyes were tested and followed. The results of the fellow eye testing were used as a safety measure (treatment failure could occur in the less affected eye) and as a secondary outcome variable. Both eyes were evaluated for progression after each visit as part of data and safety monitoring.

**Secondary Outcomes: Quality of Life Assessment: Rationale**

Quality of Life (QOL) instruments were incorporated into the IIHTT based on studies showing a substantial impact of IIH in multiple domains, including depression, physical functioning, role functioning, bodily pain and general health compared with weight-matched controls (8), neuro-ophthalmologic controls, and disease-free individuals.

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**TABLE 1. Inclusion and exclusion criteria for IIHTT**

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
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<tr>
<td>1. Age 18–60 years at the time of diagnosis</td>
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<tr>
<td>2. Diagnosis of IIH by modified Dandy criteria (6)</td>
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<td>a. LP opening pressure &gt;250 mm CSF with normal CSF contents</td>
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<td>If opening pressure 200–250 mm CSF, at least one of the following:</td>
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<td>i. Pulse-synchronous tinnitus</td>
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<td>ii. Abducens nerve palsy</td>
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<td>iii. Grade II papilledema</td>
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<td>iv. No evidence of pseudopapilledema</td>
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<td>v. Lateral sinus stenosis or collapse on MRV</td>
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<td>vi. Partially empty sella with unfolded periorbital nerve CSF spaces</td>
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<td>b. Bilateral papilledema</td>
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<td>3. Reproducible visual field loss on automated perimetry with an average perimetric mean deviation –2 to –7 dB in the worst eye</td>
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<td>4. Able to provide informed consent</td>
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<td>5. Agree to use an acceptable form of birth control during the intervention phase of the study if of childbearing potential</td>
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<th>Exclusion criteria</th>
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<tr>
<td>1. Treatment for IIH for more than 2 weeks with any agent (acetazolamide was permitted for 1 week; 1 day of washout was required for every day of acetazolamide treatment before the screening visit)</td>
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<td>2. Previous surgery, endovascular procedures, or bariatric surgery for IIH treatment</td>
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<td>3. Abnormalities on neurologic examination aside from papilledema and its related visual loss or abducens nerve paresis</td>
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<td>4. Abnormal CT or MRI (e.g., intracranial mass, hydrocephalus, dural venous sinus thrombus, or arteriovenous malformation) except for an empty sella, unfolded optic nerve sheaths, flattened sclera, or smooth-walled venous sinus stenosis</td>
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<td>5. Opening pressure &lt;200 mm CSF (a repeat CSF pressure measurement was allowed if the first LP was normal, improperly performed, or no opening pressure was obtained)</td>
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<td>6. Exposure to an oral drug, substance, or disorder that has been associated with elevation of intracranial pressure within 2 months of diagnosis (lithium, vitamin A, tetracycline and related compounds)</td>
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<td>7. Diagnosed untreated obstructive sleep apnea</td>
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<td>8. Condition requiring diuretics, oral, intravenous or injectable steroids, or other potential pressure-lowering agents including topiramate (nasal, inhaled, or topical steroids were permitted)</td>
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<tr>
<td>9. Intraocular pressures currently &gt;28 or &gt;30 mm Hg at any time in the past; Refractive error greater than ±8.00 sphere or more than ±3.00 cylinder in either eye was ineligible if there were abnormalities on ophthalmoscopy or fundus photos related to myopia that are associated with visual loss (e.g., staphyloma, retinal thinning in the posterior pole, or more than mild optic disc tilt)</td>
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<tr>
<td>10. Hyperopia greater than +6.00 D but less than or equal to +8.00 D sphere if there was no characteristic halo of peripapillary edema as determined by the site investigator or the PRC</td>
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<tr>
<td>11. Other disorders causing visual loss except for refractive error and amblyopia including vitreous cells iritis, or optic disc drusen on examination or on previous encounters</td>
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<td>12. A known allergy to pupil dilating drops or narrow angles precluding safe dilation</td>
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<tr>
<td>13. Abnormal blood work or a medical condition associated with raised ICP or a contraindication to taking acetazolamide (severe anemia, leukopenia or thrombocytopenia, renal failure, hepatic disease, renal stones)</td>
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<td>14. Type 1 diabetes or the presence of diabetic retinopathy</td>
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<td>15. Pregnancy or unwillingness for subject of childbearing potential to use contraception during the first year of the study</td>
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<td>16. Breastfeeding mothers (unless willing to discontinue breastfeeding by the baseline visit)</td>
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CSF, cerebrospinal fluid; CT, computed tomography; ICP, intracranial pressure; IIH, idiopathic intracranial hypertension; IIHTT, Idiopathic Intracranial Hypertension Treatment Trial; MRI, magnetic resonance imaging; MRV, magnetic resonance venography; PRC, photography reading center.
Vision-related QOL, as assessed by the 25-Item National Eye Institute Visual Functioning Questionnaire (VFQ-25) also have been found to be significantly lower in individuals with IIH compared with neuro-ophthalmologic and disease-free controls (9).

In a separate pilot study, 10 women with IIH completed 2 headache questionnaires and participated in semistructured telephone interviews and focus groups to assess the content domains of the Beck Depression Inventory, VFQ-25, Patient Health Questionnaire, Migraine Disability Assessment, and Headache Impact Test (HIT-6) scales for use in future research of IIH (10). Based on their responses, the HIT-6 was selected to measure headache disability in the IIHTT.

IIHTT QOL Procedure
For vision-related QOL, the NEI VFQ 25, the 10-item Neuro-ophthalmic Supplement to the VFQ-25, and Version 2 of the Medical Outcomes Study (SF-36) were administered at study entry, 6 months, and 12 months. Other assessments included the generic health-related QOL instrument SF-36 (11) and the HIT-6 inventory, a 6-question instrument assessing the impact of headache over the preceding month (12). Participants had the option of completing QOL assessments on the Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC) Web site in advance of each study follow-up visit.

Ophthalmologic Examination
The best corrected visual acuity was measured using early treatment diabetic retinopathy study charts and a refraction protocol that was based on the strategy used in the Optic Neuritis Treatment Trial (13). Complete ophthalmologic examinations were performed. Papilledema was graded by the site investigator using the Frisén scale grade (14).

Fundus Photography
Study photographers were certified by the Photography Reading Center (PRC). Digital fundus photographs centered on the optic disc and the papillomacular area were taken at each visit and sent to the PRC to document the papilledema grade.

Cerebrospinal Fluid Pressure Measurement
In addition to the baseline LP, all participants were encouraged to have a second LP for cerebrospinal fluid (CSF) pressure measurement at 6 months for comparison.

Study Interventions
Randomized Intervention
After reviewing various options for intervention, the decision was made to study individuals with mild visual loss who were unlikely to require surgical intervention. Although it is generally the first-line medication used for the treatment of IIH in clinical practice worldwide, acetazolamide had only limited supporting literature (15–18). Case reports suggested dosing up to 4 g daily for IIH treatment (17,18). Polled members of the North American Neuro-Ophthalmology Society generally prescribed between 1– and 2 g daily, and a small number indicated that they would be comfortable using 3–4 g daily in a clinical trial setting.

Possible acetazolamide-associated adverse events were considered when designing the trial, particularly with regard to aplastic anemia and hypokalemia. Other diuretic therapy was excluded during the IIHTT based on a study of 92 patients taking acetazolamide who showed no evidence of clinically significant hypokalemia unless they were on other diuretics (19). Although aplastic anemia is idiosyncratic and unpredictable, routine monitoring of the blood count was required by the FDA and serum potassium levels were followed for safety purposes.

Eligible consenting trial participants were randomized with equal probability to acetazolamide (250 mg) or matching placebo tablets. The initial dosage of study drug was 4 tablets daily in 2 divided doses. Higher dosing frequencies were deemed too complicated for the purposes of dose titration and likely to result in decreased adherence. After the initial dosing, the participants scheduled dosage increases of 1 tablet every 6 days up to a maximum dosage of 16 tablets daily (4 g daily for those receiving acetazolamide). Those individuals who were unable to tolerate the study drug could gradually decrease the dosage to a minimum of one-half tablet daily.

Starting at the month 6 visit, participants were transitioned off study medication to open-label acetazolamide by substituting 1 acetazolamide 250 mg tablet for 1 tablet of study medication every 6 days to a final dosage of 4 g daily or to a maximally tolerated dosage. This process was incorporated to ensure that subjects who had benefited from active treatment were maintained on active treatment without revealing the initial treatment assignment. Participants who did not tolerate 1 g of acetazolamide daily could gradually decrease the dosage to a minimum of 125 mg daily. To avoid treating anyone (who may have initially been assigned to placebo) unnecessarily, any participant with grade 0–1 papilledema was tapered off the study drug but not placed on acetazolamide. However, those with grade 0–1 papilledema who had persisting headaches, pulse-synchronous tinnitus, or PMD that failed to improve were transitioned to acetazolamide.

All participants were off study drug by the month 9 follow-up visit and were seen for a study visit to ensure that their vision was stable after the transition off of study medication. After the 9-month visit, medication was prescribed by their treating physician. Unscheduled visits and unscheduled laboratory testing were performed as needed.

Intervention Provided to All Participants
A specific dietary plan and lifestyle modification program was offered to all treatment trial participants. The rationale was that offering an intervention to all potential enrollees would facilitate recruitment and retention. Regression of
papilledema and symptoms in IIH has been demonstrated with modest weight loss (20–22).

The NYONRC developed a telephone-based, uniform weight loss, and lifestyle modification intervention that could be implemented for participants recruited at sites throughout North America (23–25).

The intervention covered all 3 disciplines of weight loss and lifestyle modification, that is, nutrition, physical activity, and behavior. All participants were assigned to a weight loss coach for telephone counseling sessions and were given pedometers for measuring steps and rubberized exercise tubing for resistance exercise. Nutritional instruction included meal planning, calorie counting, portion control, fat counting, and energy density. The diet intervention was implemented in 2 phases. During the first 6 months of the study (phase 1), participants were given a 500- to 1000-calorie deficit goal using the Mifflin et al method (26) to determine their calorie needs and instructed on following a partial meal replacement (PMR) diet. Studies show that weight loss is greater for patients using PMR diets compared with reduced-calorie diets; PMR dieters lose 7%–8% body weight compared with 3%–7% for conventional dieters (27). The meal replacements were in the form of shakes, soups, and bars. Weight loss coaches guided participants who declined to use these products to pre-prepared food in the marketplace that is portion and calorie controlled. Counseling sessions with weight loss coaches occurred weekly. A goal of 10% weight decrease from baseline on average was projected during the study. We anticipated that most participants in the study would undergo a weight loss intervention. A low sodium component was included in the event that normal-weight persons entered the trial to ensure that all enrollees had dietary management.

In months 7–12 (phase 2), participants had the option to transition to a balanced-deficit diet (BDD) or continue with the PMR diet. The BDD was modeled after the Dietary Approaches to Stop Hypertension (29) and Therapeutic Lifestyle Diet of the National Cholesterol Education Program (30). This diet contained approximately 20% of calories from protein, 25%–30% from fat, and the remainder from carbohydrate. Additional information and instructions were provided on a low-energy-dense diet (31), portion control (32), and environmental influences on diet (33). Counseling sessions occurred biweekly during months 7 and 8, and monthly thereafter.

All participants were instructed to keep daily records of their food and beverage intake. A password-protected Internet message board was established for participants to use to communicate with each other as well as with the NYONRC staff. The board also contained links to educational resources. To emphasize the importance of maintaining their weight loss goal, the dietary intervention was offered to participants throughout their participation in the study, even if they were no longer taking study medication.

Study Design

Randomization
Randomization was stratified by site and included blocking to ensure balance among the treatment groups within a site after a certain number of subjects had been enrolled at that site. The order of assignment of the randomization numbers within each site was provided to a masked Data Coordination and Biostatistics Center (DCBC) information analyst so that this information could be incorporated in the web-based enrollment module. A back-up system was in place whereby sites could call the DCBC to randomize a participant manually if necessary. The only individuals with access to the treatment assignments during the trial before database lock were the unmasked programmer in the DCBC who generated the randomization plan, an unmasked statistician in the DCBC who served as a liaison with the independent Data and Safety Monitoring Board (DSMB), and unmasked staff at the Clinical Materials Services Unit (CMSU). These individuals did not communicate with any other staff involved in the trial about study-related matters.

Site Personnel and Masking
Site personnel included a site principal investigator (PI), treating sub-investigator (TSI), site coordinator, visual field technician(s), and fundus photographer(s). Sites participating in the OCT ancillary study also had an OCT technician. The PI screened study candidates and determined their eligibility. All site personnel were masked to the study drug assignment. After randomization, all inquiries pertaining to the study drug and adverse events were directed to the site coordinator and Treating Sub-investigator (TSI) to minimize possible bias of the PI to the treatment assignment. The PI was responsible for assessing the subjects for possible treatment failure during the double-masked phase of the study, and for determining whether participants would continue in the open-label phase or taper off study drug without further medication at 6 months. All laboratory data generated after the screening process were reviewed by the TSI.

Sample Size Calculation and Data Analysis Plan
Sample Size Determination
Preliminary data from the IIH Study Group were used to estimate the standard deviation (SD) of the primary outcome variable, 6-month change in PMD. Data on changes in PMD over a period of 6.4 ± 1.9 months were available for 37 patients with mild visual loss (−2 to −7 dB). In the most affected eye, the mean (±SD) change in PMD was 0.82 ± 2.35 dB. Under the assumption of an SD of 2.35, an initial sample size of 140 subjects (70 per group) was calculated to provide 90% power to detect a group difference in mean change of 1.3 dB, at a significance level of 5% (two-tailed) using a t test. The target sample size was increased to 154 subjects (77 per group) to account for an anticipated withdrawal rate of approximately 10%. Monitoring of the withdrawal rate during the trial
revealed this rate to be higher than anticipated and the final sample size was inflated to 165 subjects.

The effect size of 1.3 dB was chosen on the basis of a pilot study conducted before the trial as it reflected the minimal difference associated with a clinically significant change in the visual field. Twenty-five charts of patients with IIH with mild visual loss who had at least 5 longitudinal visual field examinations were identified. Each of 3 readers reviewed all visual fields masked to the PMD associated with the field. The criterion for a clinically significant change in the field was a priori defined as a change from the index examination, confirmed on 2 consecutive subsequent examinations, which in the opinion of the reader would require a change in therapy for the patient. Agreement among at least 2 of the 3 participating readers was required for a change to be deemed clinically significant; in fact, all 3 readers were in agreement for 23 of the 25 patients. A clinically significant change was identified in 19 of the 25 patients. At the end of this process, the PMD associated with each visual field was obtained from the patient records. The minimal change in PMD that best discriminated between those who did and did not have a clinically significant change in their visual field examination was estimated using receiver operating characteristic curve analysis. This analysis revealed that a change of 1.3 dB yielded a sensitivity of 79% (i.e., 15/19 patients who had a clinically significant change also had a change in PMD of >1.3 dB) and a specificity of 83% (i.e., 5/6 patients who did not have a clinically significant change also had a change in PMD of ≤1.3 dB).

**Statistical Analysis**

The primary analyses will be performed according to the intention-to-treat principle and will include all randomized participants. The primary outcome variable is the change from baseline to month 6 in PMD in the eye with the most severe initial visual loss at baseline. The primary statistical analysis will involve fitting an analysis of covariance model with treatment group as the factor of interest, study site as a stratification factor, and baseline PMD and papilledema grade as covariates. This model will be used to calculate a 95% confidence interval for the adjusted treatment group difference in mean response (treatment effect) at month 6, and a t test will be performed to compare the adjusted treatment group means using a 2-tailed significance level of 5%. Similar models will be used to analyze changes from baseline to months 1, 2, 3, and 4.5. These will be considered to be secondary analyses.

Missing data will be imputed using regression-based multiple imputation models. This will be applied using a regression-based imputation model (34). For participants with complete data up to a particular visit, a multiple regression model will be fit that includes the outcome at that visit as the dependent variable and outcomes at previous visits, treatment group, study site, and papilledema grade as independent variables. Separate models will be similarly constructed for each visit. Using these regression models, a missing value for a participant at a particular visit will be imputed as a draw from the predictive distribution given the outcomes at previous visits (some possibly imputed), treatment group, center, and papilledema grade. This will be done sequentially starting with the baseline visit and ending with the month 6 visit. This process will be implemented 100 times, resulting in 100 complete analysis data sets. The analyses will be performed separately for each of the 100 complete analysis data sets, and the results will be combined into 1 multiple imputation inference (estimated treatment effect and associated confidence interval and P value) (35).

This approach is appropriate for data sets that have a monotone missing data pattern. If the data set does not have this pattern, the monotone data augmentation method using Markov chain Monte Carlo methods (36,37) will be used to impute the small amount of missing data that is required to make the missing data pattern monotone before applying the multiple imputation algorithm described above.

A secondary strategy for analysis will involve the use of a repeated-measures analysis of covariance model, that is, the so-called mixed model repeated measures, or MMRM, analysis strategy (38) that includes treatment group as the factor of interest, study site as a stratification factor, and baseline PMD and papilledema grade as covariates. The model will also include terms for visit (categorical), the interaction between baseline PMD and visit, and the interaction between treatment group and visit. The covariance matrix for the within-participant observations will be modeled using an unstructured pattern.

Interactions between treatment group and selected baseline variables (age; race/ethnicity; baseline PMD; papilledema grade; weight change in the previous 6 months; and constant visual loss, scotoma, and color vision loss) will be examined separately by adding the appropriate interaction term to the primary statistical model.

Treatment effects on secondary outcome variables for efficacy that are expected to be approximately normally distributed (perhaps after data transformation) will be analyzed as described above for the primary outcome variable. For presence of headache, logistic regression (with multiple imputation for missing data) will be used to assess treatment effects. An additional analysis of the PMD outcome will be performed that includes all eyes that satisfy the criterion of having a baseline value between −2 and −7 dB. The MMRM strategy of analysis as described above will be used, except that it will also accommodate the nonzero correlation between the within-subject outcomes for the 2 eyes, where applicable.

**Study Visits**

To view a schedule of activities, view Supplemental Digital Content, Table E1, http://links.lww.com/WNO/A96.

**Screening Evaluation**

The screening process occurred at 1 or more visits over 7 days. Each treatment trial candidate had general medical
and neurologic examinations and history, height, weight, blood pressure, waist circumference, urine pregnancy test in women, complete blood count, blood chemistry panel, and blood for vitamin A and genetics studies. Participants underwent an ophthalmic evaluation, perimetry, fundus photography, and QOL assessments. An magnetic resonance imaging of the brain (within 2 months of study entry) and a diagnostic LP including opening pressure measurement with CSF cell count, glucose, and protein measurements were performed as part of routine clinical care. However, the CSF from the LP performed for the diagnosis was used for the vitamin A and sodium investigational studies when available. All enrollees were offered an initial evaluation by telephone within a week of randomization by a study weight loss counselor at NYONRC to determine the appropriate dietary intervention.

Subsequent Visits and Monitoring
Eligible consenting individuals completed the randomization process and were dispensed study medication. Follow-up visits occurred at months 1, 2, 3, 4.5, 6, 9, and 12 within a 7-day window on either side of the target date. Follow-up was performed by telephone at months 7 and 8. At follow-up, subjects were queried about their interim medical history and headache status, adverse experiences, and concomitant medications used. Their visits included assessment of vital signs (including height and weight) and waist circumference, ophthalmic examination, perimetry, and fundus photographs. Study drug was dispensed, and adherence/accountability was assessed at all visits. Electrolytes were checked at baseline and every 2 weeks during dosage escalation and at 1, 3, and 6 months. Appropriate potassium supplementation was given for hypokalemia.

At the month 6 visit, participants also had a urine sodium analysis, blood sample for vitamin A studies and storage, an additional visual field examination, QOL assessments, and Patient-Centered Assessment and Counseling for Exercise Current Status Questionnaire. All participants were asked to undergo a repeat LP at 6 months after the month 6 visual field testing.

Treatment Failures and Premature Withdrawals
Conditions for premature withdrawal from the study of randomized participants included withdrawal of consent, a request for withdrawal by the Study Director or primary care physician, pregnancy, a major protocol deviation, loss to follow-up, worsening of another pre-existing disease, intercurrent illness that interfered with the use of study medication or possibly altered the course of IIH, a major and clinically significant alteration in laboratory values after beginning the study drug, other serious safety concerns, or meeting criteria for treatment failure. The study drug was discontinued immediately in women who became pregnant. All randomized participants who discontinued taking study drug because of pregnancy or other medical conditions were nevertheless asked to return for follow-up visits; the outcomes of all pregnancies were ascertained after delivery.

Possible treatment failure at follow-up was determined as a function of the PMD at baseline as follows: if the baseline average PMD ranged from $-2.0$ to $-3.5$ dB and visual function worsened more than $2$ dB PMD from this baseline average in either eye, then possible treatment failure existed. If the baseline average PMD was between $-3.5$ and $-7$ dB and the PMD declined more than $3$ dB from this baseline average in either eye, then possible treatment failure existed.

When the VFRC suspected possible treatment failure, the site PI was notified by the DCBC within 24 hours and the worsening was confirmed with repeat visual field examination at least 1 hour but within 4 days after the original visual field examination. If the worsened PMD was confirmed, the case was referred to the Study Director to ascertain whether treatment failure had occurred. After reviewing all clinical data from the DCBC, PRC, and VFRC, the Study Director determined whether the worsening of the visual field was likely due to uncontrolled intracranial pressure and progression of IIH. If he was unable to make this determination confidently, the data, including visual fields and fundus photographs, were sent to the Adjudication Committee that consisted of 4 neuro-opthalmologists. The Chair of the Adjudication Committee also reviewed all cases determined to be treatment failures by the Study Director for additional confirmation. After confirmation was made, the study participant was classified as a treatment failure and was removed from the double-masked phase of the trial. Subsequent treatment decisions were made by the treating physician. These individuals were encouraged to return for study visits at their set times for the full follow-up period (up to 4 years). If the end point of treatment failure was not confirmed, the subject continued to be followed in the trial on study medication.

Enrollment and Long-term Follow-up
One hundred sixty-five consenting participants enrolled at 38 sites between March 17, 2010, and November 27, 2012, and month 6 visits were completed by June 15, 2013. Annual follow-up examinations will continue for a total of 5 years to determine the visual prognosis, assess headache status over time, and ascertain the long-term effect of the dietary and lifestyle intervention on weight.

CASE–CONTROL STUDY TO INVESTIGATE THE ETIOLOGY OF IIH

Objectives
In addition to the treatment trial, secondary objectives of the IHTT were to determine 1) the serum and CSF levels of potential mediators of IIH suggested by the genotyping at single-nucleotide polymorphisms (SNPs) contained within genes encoding molecules likely to be involved in
the etiology of IIH; 2) differences in vitamin A and other factors (e.g., leptin, ghrelin) related to metabolism in subjects and controls; and 3) hormone levels related to obesity and to gender in IIH cases and controls using the results of the genetic testing.

**Study Population**

Controls without IIH for genetic testing were matched as closely as possible to the participants in the randomized trial (“cases”). Each control was of age 18–60 years, had a body mass index >30 kg/m², and was the same gender and the same reported race/ethnicity as a trial participant enrolled at the site. Individuals with a history of IIH or evidence of papilledema by direct ophthalmoscopy were ineligible to serve as controls. Controls had 1 study visit to measure their height, weight, and waist circumference; complete the Berlin Questionnaire for Sleep Apnea; and submit a blood sample for genetic testing, vitamin A studies, and storage.

**Outcome Measures**

**Genetic Markers Associated with IIH**

**Rationale**

In addition to the treatment trial, the IIHTT included exploratory studies in this large cohort of patients to gain additional insight into possible causes of the disorder, including genetic factors, obesity hormones, and abnormal vitamin A metabolism (39–50). Candidate genes for a role in the pathogenesis of IIH will be investigated by conducting a nested matched case-control genetic association study in which the frequencies of intragenic SNP alleles will be compared between treatment trial participants and obese controls without IIH.

**Procedure**

The candidate genes to be screened in the IIHTT were selected because of their role in sodium homeostasis, vitamin A or fat metabolism, or as cellular mediators of sex hormone signaling. Data from the HapMap (51), UCSC (52), and dbSNP (53) databases were used to identify informative SNPs for screening. As a first step, we will genotype samples received from approximately half of all IIH subjects and non-IIH controls at SNPs located within each of the candidate genes at a <20 kb average density. One hundred ninety-two SNPs were studied. Priority will be given to SNPs that represent changes in amino acid sequence (coding region only) that do not appear to be specific for any ethnic population and that are present with a minor allele frequency of >5%, with higher values more desirable. In the second step, variants that show a statistically significant difference (P < 0.05) between cases and controls (by Fisher exact test for rare mutations or chi-square analysis for common polymorphisms) will be validated in the second group of specimens from cases and controls.

**Retinol and Vitamin A Metabolism**

Retinol (vitamin A) levels were measured in both serum (151 IIH cases and 17 non-IIH controls) and CSF using high-performance liquid chromatography, also allowing measurement of alpha- and gamma-tocopherol and carotenoids (alpha- and beta-carotenes, lycopene, and beta-cryptoxanthin) concentrations in the serum. Retinol-binding protein levels were determined by radioimmunoassay in serum (n = 161) and CSF (n = 107) (54). The active vitamin A metabolite, all-trans-retinoic acid, was measured in both serum (n = 174) and CSF (n = 125) using liquid chromatography-tandem mass spectrometry. Plasma/CSF pairs were available for analysis in approximately 2/3 of cases of IIH.

**OCT Ancillary Study**

**Objective**

An ancillary study was added to establish whether high-definition OCT can provide a continuous measure of structural changes of papilledema in the optic nerve head and retina that correlate with Frisén grading, visual field deficits, and low-contrast visual acuity.

**Study Population and Procedures**

Participants at 24 sites with availability of the specific high-definition OCT machine (Cirrus; Zeiss-Meditec, Inc., Jena, Germany) had volume scans of the optic nerve head and macula regions at study entry, 1, 3, and 6 months to measure the optic nerve head volume, peripapillary retinal nerve fiber layer and total retina thickness, optic nerve head shape, macula edema, and ganglion cell layer thickness. Low-contrast (2.5%) Sloan visual acuity was tested in both eyes at each study visit in which the OCT was performed. Seventy-six percent of all treatment trial participants took part in the ancillary OCT study.

**Study Organization**

**Organizational Structure**

The study was conceived and designed under the auspices of the NORDIC (see Supplemental Digital Content, Figure E1, http://links.lww.com/WNO/A95). The National Eye Institute provided support for the NORDIC Headquarters and for the DCBC. The NORDIC Chair’s Office was responsible for aspects of study site management, including site selection, contracts and budget, study committee and investigator meetings, and site monitoring visits. NORDIC maintained a Web site that included a message board for participants.

The DCBC at the University of Rochester developed, revised, and distributed the study operations manual and case report forms. The DCBC collected all the data electronically by means of an Internet connection to a secure portal and was responsible for data monitoring and data analysis. The
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Optical Coherence Tomography and Visual Field Findings in Patients With Friedreich Ataxia

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Background: To investigate the optical coherence tomography (OCT) and visual field findings in Friedreich ataxia (FRDA).

Methods: Ten eyes of 10 patients with genetically confirmed FRDA were included in this study. Twenty-two eyes of 22 age- and sex-matched volunteers served as controls. All eyes were examined with spectral domain OCT (Retinascan Advanced RS-3000; NIDEK) and Humphrey Field Analyzer (HFA II 750; Zeiss-Humphrey Systems).

Results: OCT measurements of the average peripapillary retinal nerve fiber layer (RNFL) thickness, average peripapillary retinal thickness (RT), and foveal RT showed a statistically significant difference in choroidal thickness. OCT measurements of horizontal cup-to-disc (C/D) ratio, vertical C/D ratio, and average cup area were significantly increased in patients with FRDA. Visual acuity was significantly correlated with age at onset (P = 0.021) and average RNFL value (P = 0.014). There was a significant correlation between foveal thickness and disease duration (P = 0.014). Mean RNFL thickness was significantly correlated with the severity of neurological involvement (P = 0.039). Visual field testing (VFT) revealed a generalized reduction of sensitivity in the patients.

Conclusion: Patients with FRDA may have a measurable degree of retinal thinning as determined by OCT and a generalized reduction of sensitivity in VFT. Combining structural and functional findings may be used in the follow-up of patients with FRDA.

Journal of Neuro-Ophthalmology 2014;34:118–121
doi: 10.1097/WNO.0000000000000068
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Friedreich ataxia (FRDA) is an autosomal recessive neurodegenerative disease in which impaired mitochondrial function and excessive production of free radicals play a central pathogenic role (1). It is a rare disease affecting approximately 1 in 50,000 Caucasians (2) and has been linked to genetic defects on chromosome 9q13-q1.1. Clinical features include spinocerebellar and sensory ataxia, dystarthis, hypertrophic cardiomyopathy, scoliosis, diabetes mellitus, pes cavus, hypoacusia, optic atrophy, and eye movement abnormalities (3–7).

Ocular motor abnormalities are the best characterized signs of damage to the visual system in FRDA. They include fixation instability, saccadic dysmetria, disrupted pursuit, and vestibular abnormalities. The most common manifestation is fixation instability with frequent square wave jerks. Other ophthalmic manifestations include optic neuropathy, a retinitis pigmentosa–like syndrome, and involvement of the optic radiation (3–7). Although the pathogenesis of optic neuropathy in patients with FRDA remains unclear, many hypothesis have been proposed including bioenergetic failure, oxidative stress, glutamate toxicity, abnormal mitochondrial dynamics and axonal transport, and susceptibility to apoptosis (4,8).

Optical coherence tomography (OCT) can be used to assess the retinal nerve fiber layers (RNFL) of the anterior visual pathways. Using this technique, we measured peripapillary RNFL thickness, peripapillary retinal and choroidal thickness, and foveal thickness in patients with FRDA. Functional status of anterior and posterior visual pathways was evaluated using automated visual field testing (VFT).

METHODS

Ten eyes of 10 patients with genetically confirmed FRDA diagnosis were included in this study. Twenty-two eyes of 22 healthy volunteers served as controls. All patients were recruited from the Neurology Department of Kırıkale University School of Medicine. Informed consent was obtained from all participants as well as approval from our institutional ethics committee.

During the initial visit, a full neurological examination assessed gait spasticity, tendon reflexes, muscle weakness and wasting, scoliosis, sphincter disturbances, swallowing difficulties, and visual complaints. We used the International
Cooperative Ataxia Rating Scale (ICARS) to evaluate cerebellar ataxia. The ICARS includes the following 4 subscores: posture (maximum score, 34), kinetic functions (maximum score, 52), speech (maximum score, 8), and oculomotor dysfunction (maximum score, 6), for a possible total of 100 points. Scores increased with disease severity and indicated greater neurological disability.

Each subject underwent a complete ophthalmological examination including best-corrected visual acuity, measurement of intraocular pressure, and slit-lamp examination. Refraction of each eye was obtained using an autorefractor (Topcon Auto Ref-Keratometer, Tokyo, Japan). For OCT and VFT, 1 eye was chosen randomly for each patient and each control subject. These tests were conducted by a clinician blinded to each subject’s condition, and another investigator also was blinded, reviewed the images, and reported the results independently.

All eyes were examined with spectral domain OCT (Retinascan Advanced RS-3000; NIDEK, Gamagori, Japan) using image filling software program (NAVIS-EX, NIDEK, Tokyo, Japan). This was performed in both the peripapillary area and the macula following pupillary dilation. In the peripapillary area, a circular scan centered on the optic disc (3.45 mm diameter, “disc circle” option) was used.

We quantitated the thickness of the mean peripapillary RNFL (360°), superior quadrant (46°–135°), inferior quadrant (226°–315°), nasal quadrant (136°–225°), and temporal quadrant (316°–45°). We also measured the mean peripapillary retinal thickness (RT) and average RT in the superior, nasal, inferior, and temporal quadrants, using the same image and changing the lower border to retina pigment epithelium manually. Temporal-superior-nasal-inferior thickness (TSNIT) thickness graph (ILM-RPE/BM) was displayed automatically.

Peripapillary average choroidal thickness (CT) and average CT in 4 quadrants were calculated using inverted images of the peripapillary area. Once again, a circular scan centered on the optic disc (3.45 mm diameter) was used. The scans consisted of 1,024 “A scans” with high-definition (50 HD) frame enhancement software. This instrument has a light source of 880-nm wavelength. To improve choroidal visualization, the OCT device was positioned close to the eye to visualize the inverted image on the top of the monitor (to be in closer proximity to the zero-delay line). We selected “Layer Editor” from the menu displayed. Hyper-reflective outer border of the retinal pigment epithelial layer (RPE/BM) was displayed manually, and we drew the sclerchoroidal interface manually; the perpendicular distance between the 2 layers was designated choroid thickness. TSNIT thickness graph (RPE/ BM-manual [choroid]) was displayed automatically by the software program.

In the macula, foveal thickness was measured with OCT setting: macula map X-Y (6.0 mm × 6.0 mm [256 × 256]) automatically. Glaucoma tab of the same setting was used to display ganglion cell complex (GCC) thickness map (ILM-IPL/INL) automatically. Average GCC thickness was measured in the superior and the inferior half of the macula. Subfoveal choroid thickness (SCT) was measured in OCT setting of macula line. Inverted representation of the fundus image of each eye and a 120 average B scans were used to improve visualization of the choroidal details. After drawing lower border of the choroid manually, TSNIT thickness graph (RPE/BM-manual [choroid]) and SCT were displayed. Optic nerve head properties (cup-to-disc [vertical, horizontal], disc area, and cup area) were shown automatically in OCT setting: disc map X-Y (6.0 mm × 6.0 mm [256 × 256]).

VFT was performed using Humphrey Field Analyzer (HFA II 750; Zeiss-Humphrey Systems, Dublin, CA) with central 30-2 threshold testing with full threshold strategy on the day of examination and repeated 2 weeks later. To be eligible for analysis, participants had to have a reliable second VFT (false-positive and false-negative responses <33% and fixation losses <20%). Only data from the second VFT were used for analysis.

Statistical analysis was performed with the Statistical Package for Social Sciences program. Analysis of variance was used to evaluate the statistical significance when comparing the 2 groups. In all analyses, P value <0.05 was considered statistically significant.

**RESULTS**

Ten eyes of 10 patients with FRDA (6 women and 4 men) were included in this study and 22 eyes of 22 normal volunteers (13 women and 9 men) served as controls. Mean age of the patients with FRDA was 32.1 ± 10.46 (range, 18–49) years and mean age of the control group was 30.1 ± 10.43 (range, 18–49) years. There was no statistically significant difference in both groups in terms of age (P = 0.767) and sex (P = 0.963). The mean total ICARS score was 45.48 ± 21.20 of a possible 100 points. Demographic and clinical features of patients with FRDA are shown in Table 1.

Best-corrected visual acuities were converted to logMAR units for statistical analysis. They were 0.05 ± 0.9 in patients with FRDA and 0.00 ± 0.0 in controls (P = 0.02). The mean spherical equivalent was measured as −0.94 ± 1.10 diopters in patients with FRDA and −0.82 ± 1.32 diopters in controls (P = 0.312). There was no statistically significant difference in the mean intraocular pressure between patients with FRDA and controls (P = 0.272). Slit-lamp examination demonstrated congenital ocular anomalies in 5 of the 10 patients with FRDA. Three patients had punctate cataract with focal opacities in the nuclear and perinuclear areas of both lenses. One patient had ectropion uveae and 1 had persistent pupillary membrane in each eye. Fundus examination revealed temporal optic disc pallor in 2 patients and diffuse pallor in 1. Eight of the 10 patients had cup-to-disc ratio (C/D) >0.6.

The OCT results are summarized in Table 2. There was a significant reduction in average peripapillary RNFL thickness in patients with FRDA compared with controls (P < 0.0001).
Average RNFL thickness and peripapillary RT were also statistically significantly lower in all quadrants in patients with FRDA (P < 0.0001 and P < 0.0001, respectively).

No statistically significant difference between patients with FRDA and control groups was detected for overall mean peripapillary CT and average peripapillary CT in all quadrants. Mean RT in the fovea was significantly lower in FRDA patients (P = 0.025). Mean GCC thickness in the superior and inferior macula were significantly lower in patients with FRDA (P < 0.0001 and P < 0.0001, respectively).

Measurements of horizontal C/D ratio, vertical C/D ratio, and average cup area were found to be increased in patients with FRDA (P < 0.0001, P < 0.0001, and P < 0.0001, respectively). There was no statistically significant difference in mean disc area (P = 0.227).

In patients with FRDA, average visual field mean deviation was found to be −19.59 (range, −3.46 to −32.86). We found severe visual field impairment with reduction of sensitivity in 10 eyes of 5 patients, isolated area of reduced sensitivity in 4 eyes of 2 patients, and mild reduction of sensitivity and inferior and superior arcuate defects, more prominent superiorly, in 2 eyes of 1 patient. Visual field defects were symmetric in both eyes of patients with FRDA. Glaucoma hemifield test was outside normal limits in both eyes of 4 patients, demonstrated general reduction of sensitivity in both eyes of 3 patients, and was borderline in both eyes of 1 patient.

Visual acuity was significantly correlated with age at onset (P = 0.021) and average RNFL thickness (P = 0.045). There was statistically significant correlation between foveal thickness and disease duration (P = 0.014). Mean RNFL thickness was significantly correlated with the severity of neurological involvement (total ICARS score) (P = 0.039). There was not

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**TABLE 1.** Demographic and clinical features of Friedreich ataxia patients

<table>
<thead>
<tr>
<th>Feature</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (women/men)</td>
<td>6/4</td>
</tr>
<tr>
<td>Average age, range (years)</td>
<td>32.1 (18–49)</td>
</tr>
<tr>
<td>Average age at onset, range (years)</td>
<td>13.4 (7–18)</td>
</tr>
<tr>
<td>Average disease duration, range (years)</td>
<td>18.7 (8–31)</td>
</tr>
<tr>
<td>Spinocerebellar ataxia, %</td>
<td>100 (10/10)</td>
</tr>
<tr>
<td>Dysarthria, %</td>
<td>90 (9/10)</td>
</tr>
<tr>
<td>Wheelchair bound, %</td>
<td>80 (8/10)</td>
</tr>
<tr>
<td>Cardiomyopathy, %</td>
<td>60 (6/10)</td>
</tr>
<tr>
<td>Hearing loss, %</td>
<td>50 (5/10)</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>30 (3/10)</td>
</tr>
<tr>
<td>Scoliosis, %</td>
<td>20 (2/10)</td>
</tr>
<tr>
<td>Idebenone treatment, %</td>
<td>100 (10/10)</td>
</tr>
</tbody>
</table>

---

**TABLE 2.** OCT results in patients with FRDA and controls

<table>
<thead>
<tr>
<th>OCT Parameters</th>
<th>FRDA Group</th>
<th>Control Group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>RNFL thickness (mean ± SD), μm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average thickness</td>
<td>72.7 ± 14.7</td>
<td>111.1 ± 12.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Superior average</td>
<td>90.3 ± 18.34</td>
<td>139.1 ± 12.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Inferior average</td>
<td>85.9 ± 22.1</td>
<td>141.4 ± 21.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nasal average</td>
<td>62.2 ± 11.4</td>
<td>89.5 ± 15.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Temporal average</td>
<td>53.0 ± 13.8</td>
<td>70.6 ± 12.49</td>
<td>0.001</td>
</tr>
<tr>
<td>Retinal thickness (mean ± SD), μm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average thickness</td>
<td>291.8 ± 15.5</td>
<td>337.5 ± 13.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Superior average</td>
<td>306 ± 15.1</td>
<td>361.9 ± 14.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Inferior average</td>
<td>301.4 ± 18.8</td>
<td>355.8 ± 19.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nasal average</td>
<td>262.2 ± 31.8</td>
<td>313.4 ± 13.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Temporal average</td>
<td>297.3 ± 11.8</td>
<td>319.4 ± 14.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Choroidal thickness (mean ± SD), μm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average thickness</td>
<td>178.9 ± 38.5</td>
<td>194.6 ± 52.4</td>
<td>0.404</td>
</tr>
<tr>
<td>Superior average</td>
<td>186.6 ± 50.6</td>
<td>197.7 ± 42.6</td>
<td>0.524</td>
</tr>
<tr>
<td>Inferior average</td>
<td>161.4 ± 41.1</td>
<td>188.6 ± 52.2</td>
<td>0.157</td>
</tr>
<tr>
<td>Nasal average</td>
<td>176.9 ± 27.0</td>
<td>197.1 ± 64.9</td>
<td>0.354</td>
</tr>
<tr>
<td>Temporal average</td>
<td>188.6 ± 50.0</td>
<td>201 ± 71.1</td>
<td>0.623</td>
</tr>
<tr>
<td>Foveal retinal thickness (mean ± SD), μm</td>
<td>251 ± 24.1</td>
<td>270.8 ± 21.1</td>
<td>0.025</td>
</tr>
<tr>
<td>Subfoveal choroidal thickness (mean ± SD), μm</td>
<td>360.7 ± 58.2</td>
<td>351.4 ± 53.6</td>
<td>0.661</td>
</tr>
<tr>
<td>GCC thickness (mean ± SD), μm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior</td>
<td>83.2 ± 15.4</td>
<td>106.9 ± 8.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Inferior</td>
<td>89.2 ± 13.7</td>
<td>109.2 ± 6.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cup-to-disc ratio (mean ± SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Horizontal</td>
<td>0.68 ± 0.18</td>
<td>0.43 ± 0.12</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Vertical</td>
<td>0.67 ± 0.16</td>
<td>0.42 ± 0.15</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Average cup area (mean ± SD), mm²</td>
<td>1.17 ± 0.58</td>
<td>0.51 ± 0.31</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Disc area (mean ± SD), mm²</td>
<td>2.25 ± 0.45</td>
<td>2.53 ± 0.65</td>
<td>0.227</td>
</tr>
</tbody>
</table>

FRDA, Friedreich ataxia; GCC, ganglion cell complex; OCT, optical coherence tomography; RNFL, retinal nerve fiber layer; SD, standard deviation.
a statistically significant correlation between average RNFL thickness and mean deviation on VFT ($P = 0.243$).

**DISCUSSION**

Mitochondrial diseases such as FRDA frequently manifest neuro-ophtalmologic symptoms and signs. In addition to the visual pathways, mitochondrial disorders may involve a variety of ophthalmic structures, including extracocular muscles, eyelids, and retina (9). Fortuna et al (3) have reported a slowly progressive degenerative process involving both the optic nerves and the optic radiations in patients with FRDA. They observed diffuse and progressive pattern of RNFL loss that preceded the appearance of visual field defects and was scattered over the entire pool of retinal ganglion cells. Noval et al (10) also studied peripapillary RNFL thickness in 23 patients with FRDA and found decreased peripapillary RNFL thickness. Fortuna et al (3) found positive correlations between ICARS scores and disease duration and RNFL thickness. In this study, there was a significant correlation between severity of neurological involvement (ICARS score) and RNFL thickness but not between age at onset, disease duration, or RNFL thickness. In patients with FRDA, significant loss of visual acuity appears late, although anterior and posterior visual pathway involvement may be detected early in the disease course. Mean peripapillary RNFL thickness and RNFL thickness in the 4 quadrants were significantly lower than in the control group, and these findings were in accordance with the previous studies (3,10).

Because of high resolution of spectral domain OCT, we were able to identify the different retinal layers in transfoveal scans. Noval et al (10) also performed macular analysis, although they did not perform segmentation. We manually segmented the retinal layers in horizontal scans through the middle of the fovea and measured the thickness of the various layers. Among the studies in patients with FRDA, Noval et al (10) reported normal macular thickness and RNFL of the temporal quadrant, which represents the papillomacular bundle. We found significantly lower average peripapillary and macular RT in patients with FRDA. We also measured reduced mean GCC thickness in the macular area of patients with FRDA. However, since the resolution of current OCT devices is not sufficient to separate each of the retinal layers, we cannot conclude that the thinning was solely because of degenerative changes of the ganglion cells.

Vascular pathology has been postulated to play an important pathophysiological role in neurodegenerative disease. Cerebral hypoperfusion in Alzheimer disease has been speculated as a trigger for neuronal dysfunction, whereas cerebral vascular lesions may modify clinical presentation and severity in patients with Parkinsonism (11,12). We hypothesized that there might be abnormalities in the choroidal blood flow accompanying the neural damage in the retina of patients with FRDA, so we measured CT. However, there was no significant difference in CT between controls and patients with FRDA in both the peripapillary region and the macula. The pathology in FRDA seems limited to only neural structures.

There was no correlation between average RNFL thickness and MD on VFT. This finding supports asynchronous neurodegeneration of the anterior and posterior visual pathways, as previously reported (3). Statistically significant correlation between foveal thickness and disease duration is consistent with ongoing neuronal degeneration. This progressive loss of neuronal elements likely leads to reduced neuroretinal rim of the optic discs and an increase in C/D ratio.

We are aware of limitations of VFT analysis. Motor system dysfunction and reduced reaction times may have contributed to visual field performance in our study group. In addition, the indices used to consider a visual field reliable (false-positive and false-negative rates $<$35%; fixation losses $<$20%) may be adequate for clinical practice, but they may be too high for research purposes.

In conclusion, progressive, diffuse, and asynchronous neurodegeneration limited to neuroretinal layer may be seen in patients with FRDA. Our sample size was small, and additional studies with larger patient cohorts and more advanced OCT techniques may provide further neuro-ophtalmologic insights into FRDA.

**REFERENCES**

Parainfectious Optic Neuritis: Manifestations in Children vs Adults

Daniel Rappoport, MD, Nitza Goldenberg-Cohen, MD, Judith Luckman, MD, Hana Leiba, MD

Background: Parainfectious optic neuritis may appear at any age. The aim of our report was to compare the clinical manifestations and outcomes of this form of optic neuritis between children and adults.

Methods: The study sample consisted of all patients diagnosed with parainfectious optic neuritis evaluated by 2 neuro-ophthalmology services between 2005 and 2012. Data were collected retrospectively from the medical files. Findings were compared between patients aged 0–18 years and 19 years or older.

Results: Ten children (50% female) and 8 adults (50% female) met the study criteria. Mean duration of follow-up was 29.4 months (range, 2–72 months) in the pediatric group and 14.2 months (range, 5–80 months) in the adult group. Respective rates of bilateral disease were 50% and 38%, and all patients had optic disc swelling. The associated pathogen was identified in 60% of the pediatric group, mainly Mycoplasma pneumoniae, and 75% of the adult group, in which no microorganism predominated. The interval from the febrile illness to symptom onset was 6 days (range, 1–14 days) in the pediatric group and 19.5 days (range, 14–30 days) in the adult group. Acute disseminated encephalomyelitis (ADEM) was diagnosed in 40% (4/10) of the children and none of the adults. Final visual outcome was 20/30 or better in all patients. There was a higher frequency of bilateral disease in prepubescent vs postpubescent children.

Conclusions: Parainfectious optic neuritis is associated with a favorable visual prognosis regardless of age. Children tend to manifest visual symptoms sooner after the antecedent infectious illness and more often bilaterally and in conjunction with ADEM. The causative agent is isolated less frequently in children compared with adults.

Journal of Neuro-Ophthalmology 2014;34:122–129
doi: 10.1097/WNO.0000000000000113

Optic neuritis is a major cause of visual impairment and may be due to demyelinating inflammatory and infectious etiologies (1–7). Optic neuritis associated with an infectious etiology may be due to direction invasion by the pathogen or after an infectious disease, presumably on an autoimmune basis (1). This latter setting is designated parainfectious optic neuritis.

Optic neuritis may occur at any age. The annual incidence is lower in children (0.33–1.66 per 1,000,000) than in adults (5.1 per 1,000,000) (1). The presentation also differs by age group: children more often have bilateral disease, frequently with optic disc edema (5–9). In children, after a visual illness, optic neuritis has been reported to occur in up to 66% of cases (9). Corresponding data in adults are lacking. The aim of our study was to compare the clinical manifestations, pathogenic organisms, treatment, and outcome of parainfectious optic neuritis between children and adults.

METHODS
A retrospective case series design was used. The databases of tertiary pediatric (Schneider Children’s Medical Center) and adult (Kaplan Medical Center) medical center neuro-ophthalmology services were searched for all patients diagnosed with optic neuritis from January 2005 through November 2012. The main criterion for inclusion was acute onset of optic neuritis within 1 month after an infectious disease. Only patients who underwent complete evaluation including neuroimaging were included. The presence of an infectious disease was defined by the clinical history,
laboratory findings of lymphocytosis or leukocytosis, positive serological testing in blood or cerebrospinal fluid (CSF), and positive blood or CSF culture when performed. The diagnosis of optic neuritis was based on a finding of at least one manifestation of optic nerve disease: reduced visual acuity, abnormal color vision, relative afferent pupillary defect, or visual field defect with or without optic disc edema in one or both eyes. Exclusion criteria were optic neuropathy from causes other than infection, a space-occupying lesion on brain imaging, idiopathic intracranial hypertension, and absence of evidence of infection.

The medical files and neuroimaging studies of the eligible patients were reviewed, and demographic, clinical, treatment, and outcome data were recorded. Findings were compared between patients aged 0–18 years and 19 years or older, and between prepubescent and postpubescent children, alone or combined with the adult group. The study was approved by the institutional review boards of both medical centers.

RESULTS

Twenty-four patients met the inclusion criteria, of whom 6 were later excluded because of missing hospital or follow-up data. The demographic data of the patients are shown in Tables 1 and 2. There were 10 children aged 7–16 years (mean, 12.7 years), of whom 4 were prepubescent, and 8 adults aged 19–45 years (mean, 31 years). The mean duration of follow-up was 29.4 months (range, 5–72 months) in the pediatric group and 14.2 months (range, 5–40 months) in the adult group.

The ophthalmologic findings are shown in Tables 3 and 4. Initial visual acuity was documented in 7 children, of whom 5 (71%) had acuity of 20/150 or worse, and 7 adults, of whom 6 (86%) had visual acuity of 20/40 or better. All patients had either unilateral or bilateral optic disc edema. One adult (patient 3) had a partial macular star. Systemic neurological manifestations (headache, meningitis, encephalitis) occurred in 6 children. On magnetic resonance imaging (MRI), 4 children (40%) had findings consistent with acute disseminated encephalomyelitis (ADEM) and 1 child (10%) had nonspecific white matter lesions without clinical encephalitis. In the adult group, 2 patients (25%) had nonspecific white matter lesions and 1 (12%) had lesions consistent with microangiopathic changes. None of the adults had ADEM.

Lumbar puncture demonstrated normal opening pressure in all patients. Protein and glucose levels were within normal limits in all the patients, except 2 children with meningitis, although no pathogen was identified in their CSF.

An infectious pathogen was identified by serology or culture in 6 children (60%) and 6 adults (75%) (Table 5). The main pathogen in the children’s group was *Mycoplasma pneumoniae*, found in 4 of 6 patients (67%). In the adult group, there was no common pathogen.

Four children were prepubescent. Comparison of this subgroup with the postpubescent children alone (6/10) or combined with the adults (total 14 patients) yielded no differences in any of the parameters except for a higher rate of bilateral optic neuritis disease in the prepubescent subgroup (3/4, 75%).

Corticosteroid treatment was administered to 7 children and 4 adults (Tables 1 and 2). All treated children received intravenous methylprednisolone (10 mg/kg/day) for at least 3 days. Adults received either oral prednisone (2 mg/kg/day) for 2 weeks or intravenous methylprednisolone (1 g/d) for 3 days followed by oral prednisone 60 mg/d for an additional 11 days. Final visual outcome was 20/30 or better in all patients. There was no correlation between final visual outcome and whether or not steroid treatment was given. There were no instances of recurrent optic neuritis during the follow-up period.

DISCUSSION

In our study of parainfectious optic neuritis, the gender distribution was equal in the adult group and almost equal in the pediatric group. In most previous studies of optic neuritis, a female predominance has been reported and in children, the disease affected male and female patients equally before puberty and female patients more often after puberty (1,7–9). However, in these reports, cases of parainfectious optic neuritis were included in larger patient cohort studies.

In our case series, initial visual acuity tended to be worse in children but both groups had equally good visual outcomes. These results are in agreement with previous studies (1,7,10). Nevertheless, the visual field defects were milder than expected, perhaps owing to the early diagnosis due to the acute febrile disease and early and aggressive treatment (antibiotics and steroids). Interestingly, all patients had swollen discs at presentation. This finding was not mentioned in previous reports.

Our results highlight additional differences in clinical characteristics of parainfectious optic neuritis between children and adults. Time elapsed between the febrile illness and the onset of the visual symptoms was shorter in the pediatric group. This finding might be explained by a more fulminant immune response in children, manifested by the presence of bilateral optic nerve involvement and other neurological symptoms, with or without MRI abnormalities, consistent with ADEM. This may also be the reason why more children than adults experienced bilateral optic nerve involvement. This observation has been described in pediatric optic neuritis regardless of etiology (8,10,11).

In the adult group, the diagnosis of optic neuritis days to weeks after the presumed systemic infection support the theory that parainfectious optic neuritis is due to an immunologic–inflammatory reaction (1,5–11). The rare occurrence of uveitis in these cases also may be related to this reaction.
<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, yr</th>
<th>Gender</th>
<th>Follow-up, mo</th>
<th>Side of ON</th>
<th>Preceding Infection/Pathogen</th>
<th>Time From Infection to ON (days)</th>
<th>MRI/CT Findings at Diagnosis</th>
<th>MRI/CT Findings at the End of Follow-up Treatment</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14</td>
<td>F</td>
<td>72</td>
<td>Bilateral</td>
<td>Viral meningitis (no pathogen found)</td>
<td>5</td>
<td>Lesions in thalamus: ADEM; optic nerve enhancement</td>
<td>None</td>
<td>Steroids IV</td>
</tr>
<tr>
<td>2*</td>
<td>11</td>
<td>F</td>
<td>8</td>
<td>Bilateral</td>
<td><em>M. pneumoniae</em>, febrile illness</td>
<td>14</td>
<td>Lesions in thalamus: ADEM; optic nerve enhancement</td>
<td>2 nonspecific periventricular lesions</td>
<td>Steroids IV</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>M</td>
<td>40</td>
<td>LE</td>
<td>Pansinusitis</td>
<td>1</td>
<td>MRI: no lesions</td>
<td>Not done</td>
<td>Steroids IV + oral amoxicillin</td>
</tr>
<tr>
<td>4</td>
<td>13</td>
<td>F</td>
<td>7</td>
<td>RE</td>
<td>Sinusitis; EBV IgM</td>
<td>5</td>
<td>MRI: diffuse white matter lesions, ADEM</td>
<td>None</td>
<td>Steroids IV</td>
</tr>
<tr>
<td>5*</td>
<td>7</td>
<td>M</td>
<td>9</td>
<td>LE</td>
<td>Meningoencephalitis (no pathogen found)</td>
<td>10</td>
<td>MRI: multiple white matter lesions, ADEM</td>
<td>Some lesions disappeared or became smaller</td>
<td>Steroids IV + oral cefuroxime + doxycycline + acyclovir IV</td>
</tr>
<tr>
<td>6</td>
<td>16</td>
<td>F</td>
<td>12</td>
<td>Bilateral</td>
<td>Pneumonia, <em>M. pneumoniae</em></td>
<td>5</td>
<td>MRI: multiple brain lesions, ADEM</td>
<td>None</td>
<td>Steroids IV + oral roxithromycin</td>
</tr>
<tr>
<td>7</td>
<td>14</td>
<td>M</td>
<td>18</td>
<td>RE</td>
<td>Nonspecific viral illness: brother had chicken pox (varicella) 7–10 days before (no pathogen found)</td>
<td>Unknown</td>
<td>No brain lesions; optic nerve enhancement</td>
<td>Not done</td>
<td>Steroids IV</td>
</tr>
<tr>
<td>8*</td>
<td>12</td>
<td>M</td>
<td>72</td>
<td>Bilateral</td>
<td>Nonspecific headaches, throat culture positive for <em>Streptococcus pyogenes</em></td>
<td>Unknown</td>
<td>No brain lesions</td>
<td>Not done</td>
<td>Oral penicillin</td>
</tr>
<tr>
<td>9</td>
<td>13.5</td>
<td>M</td>
<td>16</td>
<td>RE</td>
<td>Headaches, gastroenteritis; <em>M. pneumoniae</em>, IgM</td>
<td>5</td>
<td>No brain lesions</td>
<td>Not done</td>
<td>None</td>
</tr>
<tr>
<td>10*</td>
<td>12.5</td>
<td>F</td>
<td>40</td>
<td>RE</td>
<td><em>M. pneumoniae</em>, IgM; no febrile illness</td>
<td>Unknown</td>
<td>No brain lesions</td>
<td>Not done</td>
<td>Oral azithromycin</td>
</tr>
</tbody>
</table>

*Prepubescent children.

ADEM, acute disseminated encephalomyelitis; CT, computed tomography; EBV, Epstein–Barr virus; F, female; LE, left eye; M, male; MRI, magnetic resonance imaging; ON, optic neuritis; RE, right eye.
<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, yr</th>
<th>Gender</th>
<th>Follow-up (months)</th>
<th>Side of ON</th>
<th>Preceding Infection/Pathogen</th>
<th>Time From Infection to ON (days)</th>
<th>MRI/CT Findings at Diagnosis</th>
<th>MRI/CT Findings at End of Follow-up Treatment</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27</td>
<td>M</td>
<td>6</td>
<td>Bilateral</td>
<td>Febrile illness, CMV IgM</td>
<td>28</td>
<td>Enlarged lateral ventricles</td>
<td>None</td>
<td>Vitamin B12 (because of deficiency)</td>
</tr>
<tr>
<td>2</td>
<td>23</td>
<td>F</td>
<td>5</td>
<td>LE</td>
<td>Gastroenteritis, CMV IgM</td>
<td>21</td>
<td>No abnormalities</td>
<td>Not done</td>
<td>Steroids IV and then oral</td>
</tr>
<tr>
<td>3</td>
<td>24</td>
<td>M</td>
<td>7.5</td>
<td>RE</td>
<td>Headache, Coxiella burnetii/Q fever, IgM</td>
<td>14</td>
<td>One nonspecific white matter lesion</td>
<td>Not done</td>
<td>Oral doxycycline</td>
</tr>
<tr>
<td>4</td>
<td>19</td>
<td>F</td>
<td>5</td>
<td>Bilateral</td>
<td>Nonspecific febrile illness (no pathogen found)</td>
<td>14</td>
<td>Optic nerve thickening, no enhancement, no brain lesions</td>
<td>Not done</td>
<td>Oral steroids</td>
</tr>
<tr>
<td>5</td>
<td>34</td>
<td>M</td>
<td>6</td>
<td>LE</td>
<td>Nonspecific febrile illness (no pathogen found)</td>
<td>28</td>
<td>Nonspecific white matter lesions</td>
<td>Not done</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>45</td>
<td>M</td>
<td>30</td>
<td>RE</td>
<td>Uveitis: posterior; HBV: HBCAg, HBeAb</td>
<td>At same time of uveitis</td>
<td>White matter lesions: periventricular and supraventricular (microangiopathic changes)</td>
<td>Not done</td>
<td>Oral steroids + lamivudine + steroid eye drops</td>
</tr>
<tr>
<td>7</td>
<td>32</td>
<td>F</td>
<td>40</td>
<td>RE</td>
<td>Fever, Toxoplasma IgM</td>
<td>28</td>
<td>No abnormalities</td>
<td>Not done</td>
<td>Oral clindamycin + pyrimethamine + sulfadiazine + leucovorin</td>
</tr>
</tbody>
</table>

CMV, cytomegalovirus; F, female; HBcAg, hepatitis B core antigen; HBCAb, hepatitis B E antibody; HBV, hepatitis B virus; LE, left eye; M, male; ON, optic neuritis; RE, right eye.
# TABLE 3. Ophthalmologic findings in children with parainfectious optic neuritis

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Optic Disc Edema</th>
<th>Optic Disc Edema</th>
<th>Visual Acuity</th>
<th>Dyschromatopsia</th>
<th>RAPD</th>
<th>VF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At Onset</td>
<td>At End of Follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Bilateral</td>
<td>Bilateral temporal pallor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Bilateral</td>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>LE</td>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>RE</td>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>LE</td>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Bilateral</td>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>RE</td>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Bilateral</td>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>RE</td>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>RE</td>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Optic Disc Edema**
- **RE**: Right Eye
- **LE**: Left Eye
- **LP**: Light Perception
- **FC**: Finger Counting

**Visual Acuity**
- **RE**: Right Eye
- **LE**: Left Eye
- **VF**: Visual Fields

**Dyschromatopsia**
- **NA**: Not Available

**RAPD (Relative Afferent Pupillary Defect)**
- **Binasal Constriction**
- **LE Superior Field Defect**
- **Central Scotoma + Superonasal Constriction**
- **Enlarged Blind Spot**
- **Normal**

**VF (Visual Fields)**
- **Generalized Depression**
- **Normal**

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FC, finger counting; HM, hand motion; LE, left eye; LP, light perception; NA, not available/not checked at onset due to peer condition; RAPD, relative afferent pupillary defect; RE, right eye; VF, visual fields.
### TABLE 4. Ophthalmologic findings in adults with parainfectious optic neuritis

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Optic Disc Edema</th>
<th>BCVA</th>
<th>Dyschromatopsia</th>
<th>RAPD</th>
<th>VF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RE</td>
<td>LE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Bilateral</td>
<td>20/40</td>
<td>20/25</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>LE</td>
<td>20/20</td>
<td>20/30</td>
<td>LE</td>
<td>LE</td>
</tr>
<tr>
<td>3</td>
<td>RE</td>
<td>20/20</td>
<td>20/20</td>
<td>RE</td>
<td>RE</td>
</tr>
<tr>
<td>4</td>
<td>Bilateral</td>
<td>20/200</td>
<td>20/60</td>
<td>Bilateral</td>
<td>RE</td>
</tr>
<tr>
<td>5</td>
<td>LE</td>
<td>20/40</td>
<td>20/40</td>
<td>Bilateral</td>
<td>LE</td>
</tr>
<tr>
<td>6</td>
<td>RE</td>
<td>20/40</td>
<td>20/20</td>
<td>RE</td>
<td>RE</td>
</tr>
<tr>
<td>7</td>
<td>RE</td>
<td>20/40</td>
<td>20/20</td>
<td>RE</td>
<td>RE</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Optic Disc Edema</th>
<th>BCVA</th>
<th>Dyschromatopsia</th>
<th>RAPD</th>
<th>VF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RE</td>
<td>LE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>RE mild elevation</td>
<td>20/25</td>
<td>20/20</td>
<td>No</td>
<td>No</td>
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<tr>
<td>2</td>
<td>Normal</td>
<td>20/20</td>
<td>20/20</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>Normal</td>
<td>20/20</td>
<td>20/20</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Normal</td>
<td>20/20</td>
<td>20/20</td>
<td>No</td>
<td>RE</td>
</tr>
<tr>
<td>5</td>
<td>Normal</td>
<td>20/15</td>
<td>20/15</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>RE: disc pallor</td>
<td>20/30</td>
<td>20/20</td>
<td>No</td>
<td>No</td>
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<tr>
<td>7</td>
<td>Normal</td>
<td>20/20</td>
<td>20/20</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

BCVA, best corrected visual acuity; LE, left eye; NA, not available/not checked due to general deteriorated condition; RAPD, relative afferent pupillary defect; RE, right eye; VF, visual fields.
We were able to identify an infectious pathogen in 6 children (55%) and 6 adults (75%). The majority of the culture studies in the pediatric group (67%) grew *M. pneumoniae*; 2 of these cases were associated with ADEM. Among the adults with a positive culture, we did not find a common pathogen, which is consistent with the previous reports (3,4,7,11,12).

Neurological complications of *M. pneumoniae* infection in children include encephalitis and ADEM (12–21). *Mycoplasma* also has been associated with optic neuritis in children and adults (17–20). In our study, half of the children infected with *Mycoplasma* had bilateral disease, an observation described previously, especially in patients with other neurological involvement such as encephalomyelitis (16–20).

One child in our study (Table 1, patient 4) had Epstein–Barr virus–related sinusitis 5 days preceding the development of unilateral optic neuritis and ADEM. Our search of the literature yielded only one previous case report of a child with bilateral parainfectious optic neuritis related to Epstein–Barr virus infection (22). There are also reports of 4 adults, 3 of whom had concomitant systemic neurological disease (23–26).

There is no consensus regarding treatment of parainfectious optic neuritis (1–8,11). In our study, children were given antibiotics and/or systemic corticosteroids more often because they had concurrent systemic disease. However, treatment was not associated with improved outcome in terms of visual acuity, visual fields, or residual optic nerve damage.

In this case series, parainfectious optic neuritis presented with optic disc swelling in 100% of the cases in both children and adults. However, we found several differences in the clinical presentation between these 2 age groups. The disease in children tends to be diagnosed earlier, presents more often bilaterally, and may be associated with ADEM. Although the causative agent was isolated less frequently in children, it tended to be consistent (usually *M. pneumoniae*). Even in the presence of negative serology and blood and CSF cultures, patients with a history and clinical presentation suggesting a preceding infection should be treated appropriately. In general, the visual prognosis is good.

We are aware of the limitations of our study. Our sample size was small, particularly the prepubescent subgroup. We attempted to exclude patients with multiple sclerosis, and none developed clinical or neuroimaging evidence of demyelinating disease. However, the follow-up period was short and brain MRI was repeated in only 5 cases. Finally, ours was a retrospective study that included potential patient selection bias and nonstandardized approaches to patient evaluation and treatment.

## REFERENCES


Optical Coherence Tomography Shape Analysis of the Peripapillary Retinal Pigment Epithelium Layer in Presumed Optic Nerve Sheath Meningiomas

Patrick Sibony, MD, Matthew Strachovsky, MD, Robert Honkanen, MD, Mark J. Kupersmith, MD

Background: Geometric morphometrics (GM) was used to compare the shape of the peripapillary retinal pigment epithelium–Bruch’s membrane (ppRPE) layer imaged on spectral domain optical coherence tomography (SD-OCT) of patients with presumed optic nerve sheath meningiomas (pONSM) and normal subjects.

Methods: We compared 2 groups: 30 normals to 10 patients (11 eyes) with pONSM. We digitized 20 equidistant semi-landmarks on OCT images of the ppRPE-layer, spanning 2500 µm on each side of the neural canal opening (NCO). Data were analyzed using standard GM techniques including a generalized least squares Procrustes superimposition, principal component analysis (PCA), thin-plate spline, and permutation statistical analysis to evaluate differences in shape. We also analyzed other variables with respect to shape including tumor size-proximity to the globe, age, retinal nerve fiber layer, and optic disc height.

Results: All pONSM patients were female (age 37–66 years); 10 had unilateral and 1 had bilateral optic nerve involvement. Ten of the eyes of the patients with optic disc edema at presentation, 4 went on to develop shunt vessels, and 4 had optic atrophy. The ppRPE-layer bordering the NCO in normals is V-shaped pointing away from the vitreous; the ppRPE-layer in pONSM is indented causing an inverted-U shaped deformation skewed nasally toward the vitreous. PCA showed a significant difference between normals and pONSM (permutation, n = 10,000, P = 0.001). The size and proximity of the tumor to the globe correlates with the shape of the ppRPE-layer (r = 0.75, P = 0.04). Correlation between shape variables and RNFL thickening (r = 0.51), optic disc height (r = 0.67), and age (r = 0.67) were not statistically significant.

Conclusion: The shape of the RPE layer in pONSM is characterized by an inverted-U shape or indentation that differs significantly from normals. It is indistinguishable from the shape we previously reported in papilledema and is not caused by disc edema. The mechanism in pONSM is unknown but may involve a change in the compliance of the nerve and/or localized sequestration of cerebrospinal fluid in the distal optic nerve sheath.

doi: 10.1097/WNO.0000000000000107

Spectral domain optical coherence tomography (SD-OCT) is a useful way of imaging the surface of the optic disc and peripapillary retina in a variety of optic neuropathies. For example, the average thickness of the retinal nerve fiber can be used to assess the degree of optic disc edema (1–5). The SD-OCT can also image subsurface structures such as the peripapillary retinal pigment epithelium–Bruch’s membrane (ppRPE) layer and choroid. Histomorphometric studies and in vivo imaging in animals and humans have shown that a chronic increase in the intraocular pressure can posteriorly displace the peripapillary sclera and lamina cribosa (6–13). Conversely, increased intracranial pressure can deform the sclera and ppRPE-layer anteriorly toward the vitreous (14,15). In extending this line of study, we analyzed the shape of the ppRPE-layer in patients with presumed meningiomas of the optical nerve sheath (pONSM) to characterize the shape deformation and identify tumor-related factors that might affect this deformation.

METHODS

We used geometric morphometrics (GM) to quantitatively analyze the shape of the ppRPE-layer imaged on the
SD-OCT raster. GM defines shape as the geometric property of a form that remains after filtering out variations in position, scale, and orientation. It is a well-established technique developed to quantify and statistically analyze variation in the shape of biological forms and their covariation with other variables using conventional multivariate statistical methods (16–19). It has been extensively used in the fields of biology, anthropology, and paleontology.

The analytic techniques used in GM are complex but accessible using a variety of software applications that are widely available. For those readers who wish to learn more, Sanfilippo et al (18,20) provide an overview of shape analysis that includes a discussion of GM and its application in assessing the shape of the optic cup in glaucoma. More detailed information can be found in the monograph by Zelditch et al (16) and a Web site published elsewhere (15) and described below. This study was approved by the SUNY Stony Brook Committee on Research Involving Human Subjects.

Patients

We analyzed 11 eyes from 10 patients with a diagnosis of pONSM. The presumptive diagnosis was based on both clinical and magnetic resonance imaging (MRI) findings, which consisted of unilateral (9 cases) or bilateral (1 case) slowly progressive vision loss, signs of optic neuropathy (with optic disc edema or optic atrophy), and enlargement and enhancement of the prechiasmal optic nerve sheath on magnetic resonance imaging. None of the cases were confirmed pathologically. The demographics and key clinical findings are summarized in Figure 1. We compared these patients to 30 normal eyes. Among normals, we excluded any patients with abnormal acuity, color vision, a relative afferent pupillary defect, elevated intraocular pressure; abnormal visual fields, ophthalmoscopic findings or SD-OCT evidence of an optic neuropathy, optic atrophy, glaucoma, or congenital disc anomalies (e.g., drusen, hypoplasia, oblique insertion, tilting, high myopia, staphylomas, or otherwise dysplastic).

Image Acquisition

SD-OCT were acquired with a Cirrus SD-OCT (Carl Zeiss Meditec, Inc, Dublin, CA). Sharply focused uniformly illuminated images centered over the optic nerve head were obtained using 2 standard protocols: (1) optic disc cube 200 × 200 and (2) a 5-line horizontal high definition raster (9 mm long, 0.25 mm intervals). The raster scan was positioned through the central portion of the optic disc with signal strength of ≥7. Images were saved in the highest quality .jpeg format. To more accurately assess the image (shape), we converted the display aspect ratio from 3:2 (750 × 500 pixels) (Fig. 2A, C) to a true aspect ratio of 9:2 (750 × 167 pixels) (Fig. 2B, D), which has a uniform spatial scale along both vertical and horizontal dimensions.

Digitizing Structural Semi-landmarks

Imaging software (Photoshop; Adobe Systems, San Jose, CA) was used to superimpose a transparent line grid spanning 2500 μm on either side of the neural canal opening (NCO). The grid was positioned parallel to the flattest portion of the ppRPE-layer on both sides of the NCO, with a starting reference point positioned at the innermost termination of the ppRPE-layer. The grid was used to position 10 semi-landmarks (slightly less than 278 μm apart) along the posterior border of the ppRPE-layer on the temporal and nasal side of the NCO. Points 1 to 10 were placed temporally and 11 to 20 nasally. Left eye images were flipped horizontally so that all shape figures depict the nasal RPE on the right side of the image; the temporal RPE is located on the left side (Fig. 2B).

Geometric Morphometric Analysis

We used GM tps software (19) to analyze the digitized semi-landmarks for each subject including tpsUtil, tpsDig2,
tpsRegr, and tpsPLS. The software performs a generalized least squares Procrustes superimposition which normalizes the shapes by filtering out differences in location, size, and rotation; a thin-plate spline that uses an algorithm to depict shape differences as a smooth deformation of one shape into another and generates shape variables that can be analyzed with conventional multivariate statistical methods; and principal component analysis (PCA) to identify and display the main sources of shape variance between subjects.

**Generalized Least Squares Procrustes Superimposition**

Generalized least squares Procrustes superimposition is the iterative process of estimating a mean shape and then superimposing all of the objects onto this mean shape. This is performed in 3 steps (16). First, the set of points for each subject is adjusted so that their centroid (mean of all of the x coordinates, mean of all the y coordinates) is translated to the origin. This is done by subtracting centroid coordinates from the coordinates of each landmark. Second, each configuration is scaled by dividing by the centroid size (the square root of the summed squared distances of each landmark from the centroid of its landmark configuration). Third, rotational differences are removed by iteratively minimizing the summed squared distances between corresponding landmarks.

**Thin-Plate Spline**

The thin-plate spline has 2 important functions. First, it is used to depict shape differences as a smooth deformation of one shape into another using an algorithm that interpolates potential changes between landmarks of a reference shape (the mean shape) and the shape it is being compared with. These same shape differences can also be visualized using vectors at each landmark showing the magnitude and direction of the differences at each landmark.

The thin-plate spline is also used to define a set of shape variables, partial warps, that capture the shape differences among the objects being compared. The partial warp scores provide data matrices that can be analyzed with conventional multivariate statistical methods.

**Principal Component Analysis**

Because shape variation is multidimensional, PCA was used to express as much of the variation as possible in just a few dimensions that are linear combinations of the partial warps. This allows one to identify and display most of the variation in shape between subjects. The relative contribution of each dimension is proportional to its variance. The tpsRelW software was used for these computations.

**Statistical Analysis**

A test statistic adapted to assessing shape differences was proposed by Goodall (16,21). It compares sums of squared Procrustes differences between and within the samples being compared and expresses it as an F-ratio. Valid statistical tests can be made by comparing the observed F value to an empirical distribution based on a large number (10,000

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**FIG. 2.** Spectral domain optical coherence tomography (SD-OCT) 9 mm-raster comparing a normal eye from signature case 1 with a presumed optic nerve sheath meningioma illustrating the corrections for aspect ratio, semi-landmark placement and an example of the inverted-U shape and V-shape referred to in the text. A. Normal subject SD-OCT raster scan using the standard jpg image output (9 mm; aspect ratio of 3:2; 750 × 500 pixels). Note that the vertical (300 μm) and horizontal (900 μm) box scale differ, resulting in a 3-fold vertically stretched image. This image demonstrates the V-shape of the retinal pigment epithelium–Bruch’s membrane (RPE) layer that gently slopes away from the vitreous typically seen in normal subjects. B. Corrected 9-mm image that eliminates vertical stretch by adjusting the vertical scale to reflect the actual shape of the peripapillary eye wall. The image correction, used in our analysis of shape, has an aspect ratio of 9:2 (750 × 167 pixels). The numbered points demonstrate the placement of 10 equidistant semi-landmarks that define the shape of the RPE (starting at the border of the NCO) and spanning 2500 μm on the nasal and temporal side of the neural canal. C. Signature case 1 of a patient with a presumed optic nerve sheath meningioma (9 mm, 3:2 aspect ratio; 750 × 500 pixels). The yellow arrows outline the inverted U-shape deformation, in this case severely indenting the globe toward the vitreous. D. The same case 1 after image correction (9 mm, aspect ratio to 9:2, 750 × 167 pixels).
in this study) of random permutations of the assignments of individuals to the groups being compared. The proportion of Goodall’s F statistics from permuted data sets that are equal to or larger than the observed Goodall’s statistic is interpreted as the probability value for the test. Goodall’s F test only considers the total amount of shape variation and does not display the nature of the differences.

For traditional morphometric measurements, for example, disc elevation, average RNFL, and NCO diameters, we used Student t test and analysis of variance where appropriate. We analyzed how shape variables might covary with a variety of factors including age, refractive error, RNFL thickness, elevation of the optic disc, overall length of the tumor (size), and its proximity to the globe. Correlation between shape variables and RNFL, disc height, age, and tumor size and proximity to the globe were assessed using a Partial least squares analysis (using J Rohlf’s tpsPLS software). MRI was used to measure the (1) length of the tumor and (2) proximity to the globe (measured as the distal leading edge of tumor to the posterior wall of the globe in millimeters). We also used an algorithm that combined the length of the tumor with a weighted score that was based on its proximity to the globe. For example, tumors <2 mm from the globe received 20 points in addition to the length of the tumor, <5 mm received 10 additional points, <10 mm received 5 additional points, and so on.

RESULTS

Ten women with presumed ONSM between the ages of 37–66 years (mean, 48.7 years) were followed over an average of 58 months (range, 32–141 months). Nine of the patients had a unilateral lesion, 1 patient had bilateral involvement, with 7 right eyes and 3 left eyes (Fig. 1). At presentation, 10 of the eyes had optic disc edema, 1 had optic atrophy. Four of the eyes went on to develop optic atrophy. Four went on to develop retinochoroidal venous collaterals (optociliary shunt vessels). The pONSM of 2 patients showed calcification on computed tomography (CT). The MRI in all cases showed thickening or enlargement of the optic nerve with enhancement, usually along the optic nerve sheath. The greatest deformation was associated with meningiomas abutting the globe, although shape deformation was also observed among patients with tumors remote from the globe. There was one exception with a normal shape in a patient where the tumor was distant from the globe. There was one exception with a normal shape in a patient where the tumor was distant from the globe.

OCT data at presentation were not available in 4 of the cases. However, after a mean follow-up of 58 months, data from the most recent visit showed that the mean RNFL thickness was distributed bimodally. Those with chronic disc edema averaged 156 μm (±44 μm), and those with optic atrophy averaged 67.4 μm (±6.5 μm). The unaffected eye averaged 92.6 μm (±8.9 μm) compared with normal subjects with a mean of 92.2 μm (±9.6 μm).

A generalized Procrustes superimposition of 20 semi-landmarks for 41 patients (30 normal optic discs and 11 pONSM eyes) is shown in the scatter plot (Fig. 3A). The consensus or mean shapes of the Procrustes transformed semi-landmarks for each group are shown in Figure 3B demonstrating the differences in the shape of the ppRPE-layer in normals vs pONSM. Note that these shapes were obtained from images with an aspect ratio 9:2. However, the horizontal raster images shown in Figure 1 are displayed as they are generated by the Cirrus SD-OCT with a 3:2 aspect ratio.

Our results demonstrate that the mean ppRPE-layer in normals has a V-shaped configuration sloped outwardly (away from the vitreous) as it approaches its central margin at the NCO. In contrast, the consensus (mean) shape for subjects with pONSM have an inverted-U shaped ppRPE-layer that is anteriorly displaced toward the vitreous. There is slight nasal skew in the inverted-U shape compared with the relatively symmetrical V-shape in normals. The difference between the 2 groups was highly significant at $P = 0.001$ (permutation statistics). Two examples of a normal V-shaped RPE layer and an inverted U-shape RPE layer are illustrated both in the uncorrected (3:2 aspect ratio) and corrected (9:2 aspect ratio) forms in Figure 2. Figure 1 displays each of the uncorrected raster scans (3:2 aspect ratio) from both the affected and the contralateral unaffected eye for comparison. The deformations vary from an obvious inverted U-shape indentation of the globe (e.g., 1–5) to mild relative flattening of the globe compared with the normal side (e.g., 6–10). There is no apparent deformation in patient 11 who had the smallest tumor furthest from the globe.

A variance—covariance matrix of the shape variables derived from both groups of patients was used to perform a PCA (using tpsRelW software (19)). The first 2 principal components together account for 81% of the variance; 62% from PC1 alone. Figure 4 shows the distribution of principal component scores from each subject along the first 2 PC axes. The shape implied along the PC1 axis depicts a continuum of shapes that ranges from an inverted-U (on the negative side of the abscissa) to a V-shape (on the positive side of the abscissa). The PC2 along the ordinate describes a shape change that goes from NCO contraction (up-in) on the negative side to NCO expansion (down-out) on the positive side (Fig. 4). The intersection of PC1 and PC2 represents the consensus shape of the ppRPE-layer semi-landmarks for all specimens. The PC plot shows 2 distinct clusters (pONSM and normals) that segregate along PC 1. With one notable exception (patient 11), nearly all subjects with pONSM exhibit some degree of the inverted-U shape deformation to relative flattening compared with the normals. There was no obvious segregation of the 2 groups along PC2. The probability that this difference in shape between pONSM and normal subjects could have arisen by chance was 1 in 10,000 permuted data or $P = 0.0001$. 

There was no statistically significant correlation between shape variables and the age of the subject ($r = 0.67$), disc height ($r = 0.67$), mean RNFL (0.51), length of the tumor ($r = 0.61$), proximity of the tumor to the globe (0.66), or length + proximity ($r = 0.71$). An algorithm that assigned points based on proximity to the globe plus tumor length (in millimeters) did show a moderate correlation ($r = 0.75$, $P = 0.037$) with shape.

**DISCUSSION**

This study shows that shape of the ppRPE-layer in patients with pONSM differs from normals, and this difference was statistically significant. It is characterized by an inward deformation of the ppRPE-layer toward the vitreous that presumably reflects the shape of the underlying load bearing peripapillary sclera (15) and correlates with both the size and proximity of the tumor to the globe. Larger tumors contiguous to the sclera are associated with greater amounts of deformation. The shape of the ppRPE-layer in 1 patient with a small tumor, most distant from the globe, showed no deformation and was otherwise normal.

The peripapillary shape deformation demonstrated on the SD-OCT can, at times, be seen on an MRI, CT, or B-scan echography as flattening of the globe in some cases associated with acquired hyperopia and choroidal folds (22–28). The SD-OCT however is more sensitive and provides greater detail than the MRI and CT. The application of GM to these images can statistically distinguish shape differences from normals even when differences appear normal by gross inspection (15).

Pathologically, ONSM may infiltrate the optic nerve head and the adjacent choroid (29–31). Shape deformation in such instances probably is due to direct compression of the optic nerve with axonal flow blockade and proximal swelling, in much the same way that an intracranial orbital

**FIG. 3.** A. Scatter plot shows semi-landmarks from 10 patients, 11 eyes with presumed optic nerve sheath meningioma (pONSM) (black dots) and 30 normal subjects (red dots) after Procrustes superimposition (i.e., after normalizing for location, size, and rotational differences between subjects). B. Thin-plate spline compares the consensus (mean) shape of the peripapillary retinal pigment epithelium–Bruch’s membrane (ppRPE) layer in normals with those with pONSM. Nasal is positioned on the right side and temporal is on the left side of the figure. The ppRPE-layer in pONSM has an asymmetric inverted-U shape that is inwardly bowed toward the vitreous and skewed nasally. Normals have a relatively symmetrical outward V-shaped RPE layer directed away from the vitreous.

**FIG. 4.** Principal component analysis shows that 81% of the shape variance among all subjects can be explained by the first 2 principal components (PC1, 62%; PC2, 19%). The shape implied along PC1 (absissa) displays an inverted U-shape on the negative side to a V-shape on the positive side. PC2 (ordinate) implies a radial expansion or contraction of the neural canal opening. Black-filled circles represent the PC scores of the meningioma patients and open circles represent normals. With one exception (11), the meningioma patients form a distinct cluster (oval) along the negative side of PC1. Normals are more tightly clustered along the positive side of PC1. There was no clear segregation between groups along PC2. One patient (11) had a small meningioma approximately 15 mm from the globe with no signs of shape deformation.
tumor will compress the globe and induce choroidal folds and hyperopia. However, the mass effect on the globe with most pONSM, even those contiguous to the globe, is mild by comparison. Moreover, in 5 of 11 eyes (patients 4, 7, 8, 9, and 10) the deformation was evident even when the tumor did not appear (based on MRI) to directly compress the globe. Taban et al (28) have described a patient with remote parasellar meningioma involving the optic canal and orbital apex, who exhibited choroidal folds and flattening of the globe by B-scan ultrasound.

The mechanism by which an ONSM can deform the globe is unknown. It is noteworthy that the shape deformation in pONSM is indistinguishable from the shape of the ppRPE-layer in patients with intracranial hypertension and papilledema. Eight eyes of our patient cohort had optic disc edema at presentation. However, disc edema alone does not explain these shape deformations because we have previously shown that there is no shape deformation in patients with disc edema due to anterior ischemic optic neuropathy (15). In an animal model, Morgan et al (7) have shown that displacements of the optic disc surface is probably the result of translaminar pressure differences between the subarachnoid and intracranial fluid compartments. This is the likely explanation of the subsurface deformations at the level of the ppRPE-layer in patients with papilledema (15,32).

There are a number of similarities in the clinical signs of both chronic papilledema and pONSM. Patients with papilledema initially present with bilateral or asymmetric disc edema, normal acuity and color vision, and enlargement of the blind spot on visual fields. Likewise, patients with meningiomas of the optic nerve sheath present early on with isolated unilateral optic disc edema, normal acuity, and enlargement of the blind spot, and then slowly progress with loss of peripheral visual field, and eventual optic atrophy and shunt vessels on the disc surface (33–36). In the absence of a large intracranial tumor component, patients with isolated intraorbital pONSM do not have intracranial hypertension. The clinical similarities in their effects on the nerve head between chronic papilledema and pONSM may be a consequence of the underlying biomechanics common to both of these entities.

Some investigators (37–43) have suggested that the cerebrospinal fluid (CSF) in the periotic subarachnoid space (poSAS) may not freely communicate with the intracranial subarachnoid space based on measurable concentration gradients of CSF proteins and contrast along the optic nerve sheath. This concentration gradient has similarly been demonstrated in a patient with an ONSM (38). It is possible that the shape differences in pONSM are the result of localized increased pressure within the poSAS because the tumor effectively functions as a one-way hydraulic valve.

The biomechanical effects of the meningioma on the optic nerve sheath may also play a role. Strain is a measure of local deformation of a material or tissue induced by stress (applied force per cross-sectional area). The amount of strain is also influenced by the material properties of the tissue; that is, its ability to resist deformation (stiffness or compliance). Normally, the intraorbital segment of the optic nerve is slack and compliant; the ends fixed within the neural canal and the annulus. Eye movements stress and strain the nerve and the peripapillary eye wall. Thickening, calcification, and increased pressure in the poSAS in patients with meningiomas presumably stiffen the optic nerve sheath. This decrease in compliance may also contribute, if not cause, the deformation observed on OCT.

The functional significance of this deformation is unknown. Burgoyne et al (13) have suggested that distortions of the laminar pores and surrounding sclera, in glaucoma at least, may impede axoplasmic transport and blood flow that ultimately affects axonal and glial function within the optic nerve head. This may play an important role in papilledema and pONSM with disc edema because the magnitudes of shape differences are substantially greater than they are in glaucoma (15).

Regardless of the underlying mechanism, recognition of peripapillary deformation of the ppRPE-layer on the SD-OCT may be helpful in selected cases. Examples include distinguishing pseudopapilledema from true disc edema, detection of infiltration optic nerve sheath tumors in patients with disc edema or retinal vein occlusions, and assisting to identify shunt failure particularly in patients with optic atrophy.

REFERENCES


Congenital Fixed Dilated Pupils Due to ACTA2—Multisystemic Smooth Muscle Dysfunction Syndrome

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Abstract: Congenital fixed dilated pupils (congenital mydriasis) is characterized by hypoplasia or aplasia of the iris muscles, with absence of iris between the collarette and pupillary border, creating a scalloped pupillary margin. This condition has been reported in a multisystemic smooth muscle cell dysfunction syndrome, combined with congenital patent ductus arteriosus, cerebrovascular disease (Moya-moya-like), coronary artery disease, thoracic aorta aneurysm, and dysfunction of smooth muscle cells in organs throughout the body. All affected individuals carry a p.R179H heterozygous mutation in the ACTA2 gene. We add to the ophthalmologic involvement with 3 more patients. Congenital fixed dilated pupils is a rare condition and should alert ophthalmologists to the possibility of the coexistence of systemic life-threatening disorders.

CONGENITAL FIXED DILATED PUPILS

Congenital fixed dilated pupil, sometimes referred to as congenital mydriasis, or partial aniridia, is a rare ophthalmic condition. Hypoplasia or aplasia of the iris sphincter and dilator muscles results in fixed dilated pupils from birth, with no reaction to light, convergence, pilocarpine, tropicamide, or phenylephrine. The iris is described as hypotrophic, often with a persistent pupillary membrane. Although iris morphology is pathognomonic, it has sometimes been misdiagnosed as aniridia.

In 2010, Milewicz et al (1) reported a severe and highly penetrant phenotype with congenital fixed dilated pupils, cardiovascular and cerebrovascular abnormalities, and multisystemic smooth muscle dysfunction, associated with the p.R179H mutations of the ACTA2 gene.

We describe 3 unrelated young girls with congenital fixed dilated pupils observed since birth, associated with progressive neurological deterioration and smooth muscle cell (SMC) dysfunction.

CASE REPORT

Case 1

A 19-year-old girl, the fourth child of healthy nonconsanguineous parents, had an unremarkable antenatal birth history. Congenital mydriasis, with absence of direct and consensual pupillary light reflexes, was observed in the first day of life, and agenesis of the left toes and syndactyly of 2 toes of the right foot. Patent ductus arteriosus was surgically repaired at 1 year of age. Initial development was normal, but the patient experienced left hemiparesis at 2 years of age. Cerebral angiography, performed at ages 2, 3.5, and 6 years, demonstrated stenosis of the supraclinoid segment of both internal carotid arteries, with a straightened course of the cerebral vessels (Fig. 1). Subsequently, the patient developed severe neurological and cognitive handicaps, including dysarthria and tetraparesis. Magnetic resonance imaging (MRI) of the brain showed diffuse cortical and subcortical ischemic lesions (Fig. 2).

As the patient became older, she developed aortic valvular dysfunction, pulmonary hypertension, and progressive vasculopathy of the aorta. She also experienced multisystemic pathologies, including constipation, gallstones, recurrent urinary tract infections, hypotonic bladder, hypothyroidism,

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The authors report no conflicts of interest.

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Roulez et al: J Neuro-Ophtalmol 2014; 34: 137-143


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deep venous thrombosis, asthma, and acute dyspnea, with multiple episodes of bronchial pneumonia.

Examination at 6 years of age revealed visual acuity of 20/50 in both eyes. Extraocular movements were full. The pupils measured 6 mm and was nonreactive to light, accommodation, 2% pilocarpine, 1% cyclopentolate, and 5% phenylephrine eye drops (Fig. 3). Ophthalmoscopy was normal. Visual function at 19 years of age was unchanged, but the fundus revealed peripheral retinal arteriolar stenosis (Fig. 4).

Because of the iris features associated with SMC dysfunction, we obtained genetic mutation analysis of the ACTA2 gene, with identification of the c.5536G>A (p.R179H) heterozygous mutation.

**Case 2**

A 14-year-old girl, the second child of nonconsanguinous parents, was born after an uneventful pregnancy. At 3 weeks of age, she underwent repair of a patent ductus arteriosus. She began to walk at an age of 15 months, but developmental delay prompted a neurologic evaluation. Her balance was unsteady, and there was mild impairment of both fine and coarse motor skills. At age 19 months, MRI showed multifocal parieto-occipital white matter lesions. At 5 years of age, the patient developed rapidly progressive loss of motor control, with dystonic gait, poor balance, and dysarthria. Brain MRI revealed numerous multiple periventricular white matter abnormalities (Fig. 5). Magnetic resonance angiography showed dilation of both proximal internal carotid arteries and stenosis of distal internal carotid arteries extending to anterior and middle cerebral arteries (Fig. 6). At 12 years of age, the patient underwent echocardiography, and an aneurysm of the ascending aorta was detected.

The patient’s mother had noted both pupils of her child had been dilated since 6 weeks of age. Ophthalmologic examination at 6 years revealed blue irides, with hypotrophic stroma, without crypts, and no iris tissue central to the pupils.

**FIG. 1.** Case 1: Anteroposterior view of subtracted cerebral angiogram shows filiform supraclinoid left internal carotid artery (long arrow), dilation of the proximal internal carotid artery (short arrow), cerebral arteries with areas of focal stenosis, and no moyamoya-type collaterals in the region of the basal ganglia.

**FIG. 2.** Case 1: Axial T2 magnetic resonance imaging reveals cortical and subcortical ischemic lesions in the distribution of both carotid arteries, predominantly in the watershed zones.

**FIG. 3.** Case 1: Fixed dilated pupil of the right eye with remnants of persistent pupillary membrane.
collarette. Filiform strands of persistent pupillary membrane projected from the collarette onto the anterior lens capsule, producing a scalloped pupillary margin (Fig. 7). Both pupils measured 6 mm, with no reaction to light or accommodation. A right esotropia was present, but extraocular movements were full. Funduscopic examination demonstrated retinal vascular tortuosity (Fig. 8). At 14 years of age, visual acuity corrected to 20/40, right eye, and 20/25, left eye, and the patient was prescribed bifocal spectacles. DNA analysis revealed a p.R179H mutation of the \textit{ACTA2} gene.

**Case 3**

A 16-year-old girl was sent for genetic testing by her ophthalmologist due to fixed dilated pupils discovered at birth. Her medical history consisted of patent ductus arteriosus, operated at 4 weeks of age, frequent respiratory and urinary tract infections, dyspnea, and deep venous thrombosis. A thoracic scan showed pulmonary emphysema, bronchiectasis, and dilation of the ascending aorta. Although no abnormalities were detected on clinical and neurologic examinations, MRI of the brain showed diffuse periventricular and deep subcortical white matter changes. Examination revealed visual acuity of 20/20 in each eye. The pupils were nonreactive, with hypoplastic irides and numerous iris strands projecting onto the anterior lens capsule (Fig. 9). Funduscopic examination demonstrated retinal vascular tortuosity. The patient was prescribed bifocal spectacles. Genetic testing of the \textit{ACTA2} gene revealed the p.R179H mutation.

**DISCUSSION**

The \textit{ACTA2} gene encodes the contractile protein alpha-actin in SMCs. Heterozygous \textit{ACTA2} mutations cause a predisposition to a variety of vascular diseases, including thoracic aortic aneurysms and dissections, early onset arteriosus, operated at 4 weeks of age, frequent respiratory and urinary tract infections, dyspnea, and deep venous thrombosis. A thoracic scan showed pulmonary emphysema, bronchiectasis, and dilation of the ascending aorta.
coronary artery disease, and strokes (2). It has been suggested that \(ACTA2\) missense mutations disrupt alpha-actin polymerization and lead to decreased contractility of aortic SMCs, which in turn leads to thoracic aortic disease (3). Occlusive disease of smaller vessels associated with \(ACTA2\) mutations is likely due to increased vascular SMC proliferation (2), resulting in stenosis or occlusion.

In 2010, Milewicz et al (1) reported 7 unrelated patients with a de novo missense mutation in the \(ACTA2\) gene (p.R179H) and multisystemic smooth muscle dysfunction syndrome (MSMDS), including aortic and cerebrovascular disease, patent ductus arteriosus, and congenital fixed dilated pupils. Möller et al (4) reported the ophthalmic features of 3 patients with MSMDS. They all presented with normal visual acuity, dilated nonreactive pupils, impaired accommodation, and retinal vascular tortuosity. In 2012, Munot et al (5) described a typical cerebrovascular phenotype with this \(ACTA2\) (p179H) mutation: stenosis of the supraclinoidal segment of both ICAs; dilation of proximal portions of the ICAs; straight course of the cerebral vessels, which also show focal stenosis; and absence of basal collaterals. This cerebrovascular phenotype is not strictly identical to moyo-moya angiopathy.

The occlusive vascular disease found in the smaller diameter arteries of these patients probably results from an increased vascular SMC proliferation in the intimal and medial arterial layers. Elastin, found in large arteries, inhibits SMC proliferation (2,5). The change in vessel caliper of the internal carotid artery, from dilation to stenosis, occurs within the cavernous portion, where there is no external elastic lamina within the vessel wall. This supports the hypothesis that abnormal SMC proliferation is modulated by arterial wall components.

Table 1 summarizes the systemic features of the reported patients with congenital fixed dilated pupils together with our 3 cases. All patients test positive for the \(ACTA2\) gene mutation (p.R179H). Severe clinical manifestations became manifest early in life. This included surgery for patent ductus arteriosus in the first year of life, and during the first 2 decades of life, aortic or great vessel aneurysms or dissections. Many also developed cerebrovascular anomalies with transient neurological deficits and stroke-like presentation. Regarding our patients, Case 1 had a stroke with a hemiparesis at 2 years of age, and Case 2 developed dystonia and dysarthria at 5 years. It is noteworthy that no neurological abnormalities were detected in Case 3 until the age of 16, although cerebral MRI showed chronic ischemic white matter changes. Indeed, white matter abnormalities have been reported in nearly all \(ACTA2\) patients and increased in number as an age-related phenomenon, reflecting occult small vessel disease (5,7).

As seen in Table 1, these patients experienced altered function of other SMC-dependent organs, including decreased contractile function of the bladder and gastrointestinal tract, resulting in hypotonic bladder, recurrent urinary tract infections, hypoperistalsism, and gallstones. Decreased SMC function of pulmonary alveoles leads to tachypnea at birth, pulmonary hypertension, asthma, bronchiectasis, and emphysema.

Reported patients with congenital fixed dilated pupils had pupil diameters ranging from 5.5 to 7 mm. The pupils were nonreactive to light and convergence, as well as a variety of topical eye drops. The marginal portion from the collarette to the pupillary border (pars pupillaris) is absent, resulting in a scalloped pupillary margin. The remaining portion of the iris (pars ciliaris) is hypoplastic with the absence of crypts, but does not transilluminate. Numerous strands of persistent pupillary membrane extend from the collarette to the anterior lens capsule. Our Case 1 had cortical visual impairment, resulting in vision reduced to 20/50 bilaterally, but otherwise distance vision is usually good in \(ACTA2\) patients. In most cases, accommodation is reported to be very poor (4,10).
<table>
<thead>
<tr>
<th>Reference</th>
<th>Gender, Age</th>
<th>Development Delay</th>
<th>Development Delay</th>
<th>CNS Abnormalities</th>
<th>Cardiovascular</th>
<th>Retinal Vascular Tortuosity</th>
<th>Systemic Involvement</th>
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<td>Milewicz 2010 (1) Case A</td>
<td>F, 12</td>
<td>Mild</td>
<td></td>
<td>WM signal changes, Moya-moya-like, infarcts</td>
<td>PDA, AAA</td>
<td>+</td>
<td>Hypotonic bladder, tachypnea at birth</td>
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<td>Khan 2004 (6) Case 1</td>
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<tr>
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<td>–</td>
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<td></td>
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<td>Milewicz 2010 (1) Case C</td>
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<td></td>
<td></td>
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<td>WM signal changes, Moya-moya-like</td>
<td>PDA, AAA, aortic coarctation</td>
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<td>Hypotonic bladder, tachypnea at birth, cystic lung, hypoperistaltism, malrotation, gallstones</td>
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<tr>
<td>Lemire 2004 (10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>RE ophthalmic artery occlusion</td>
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<td>F, 26</td>
<td>–</td>
<td></td>
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<td>PDA, AAA</td>
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<tr>
<td>Milewicz 2010 (1) Case F</td>
<td>M, 17</td>
<td>–</td>
<td></td>
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<td>WM signal changes</td>
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<td>+</td>
<td>Hypotonic bladder</td>
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<td>Richer 2012 (9)</td>
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<td>Neonatal infarcts, progressive WM anomalies</td>
<td>PDA</td>
<td></td>
<td>Hypoperistaltism</td>
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Alpha-actin is expressed in the dilator and sphincter muscles of the normal iris (11). Optical coherence tomography of the iris and biomicroscopic imaging suggests absence of the iris sphincter muscle (Fig. 10). Absence of the concentric circular folds in the peripheral iris is consistent with absence of the pupillary dilator muscle. Absence of the pupillary sphincter and dilator muscles awaits histopathologic confirmation.

Retinal arteriolar stenosis and occlusion progressively appearing in the second decade of life is similar to the occlusive arteriolar disease occurring in the brain. SMC proliferation can progressively obstruct the vessels since the elastic lamina is lacking in retinal arteriolar walls. Möller et al (4) reported retinal vascular tortuosity with increasing age, and this could be related to vessel wall changes and loss of contractility. One of his patients also developed areas of arteriolar dilation and microvascular changes with leakage. Two of our patients (Cases 2 and 3) developed retinal vascular tortuosity. These vascular abnormalities support the experimental findings of Tomasek et al (12) that alpha-actin in the pericytes and the SMCs of the retinal vessel walls is necessary for normal retinal vascular permeability and for a normal blood–retina barrier.

There are a few published reports of children with congenital mydriasis associated with isolated patent ductus arteriosis or aorticopulmonary septal defects (13–17), but screening for ACTA2 was not performed. Systemic abnormalities in these patients included abdominal aortic aneurysm and myocardial infarction in an 8-year-old girl (16) and retinal tortuosity in 2 other patients (14,15). Neurologic status was normal, but all patients were very young (oldest was 9 years of age). Association between patent ductus arteriosus and fixed dilated pupils is suggestive of MSMDS, as alpha-actin is expressed by cardiomyocytes.
during heart embryogenesis between the 9th and 33rd weeks of development (18).

Recently, congenital mydriasis has been described in 2 neonates with megacystis microcolon intestinal hypoperistalsis syndrome, in association with impaired vesical and intestinal peristalsis (19). The genetic basis remains unknown as ACTA2 screening was not performed.

In 1965, Gillespie (20) described 2 individuals with cerebellar ataxia, mental retardation, and iris abnormalities similar to those seen in our report. These patients demonstrate hypoplasia of the cerebellar vermis on MRI but do not develop cerebrovascular complications. To date, the inheritance and genetics of this disorder remain unknown.

Fixed dilated pupils in a young child is an extremely rare condition and should alert pediatricians and ophthalmologists to the possibility of the coexistence of systemic life-threatening disorders, including MSMDS. Genetic testing is essential in evaluating this patient population.

REFERENCES


Anti–NMDA Receptor Encephalitis Associated With Transient Cerebral Dyschromatopsia, Prosopagnosia, and Lack of Stereopsis

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Abstract: A 20-year-old woman suffered from anti–N-methyl-D-aspartate receptor (NMDAR) encephalitis and was treated with removal of an ovarian teratoma and retroperitoneal ganglioneuroma in addition to immunotherapy. She was incapable of face recognition, had difficulty with object recognition, and lacked color sensation and stereo perception during recovery. These symptoms were transient and completely resolved over 4 months. Our report documents additional aspects of visual impairment associated with anti-NMDAR encephalitis and suggests that the disease can lead to diffuse cerebral dysfunction including the cortical visual system.


Anti–N-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune disorder characterized by the temporal progression of a variety of clinical features including psychiatric symptoms, seizures, movement disorders, reduced consciousness, central hypoventilation, and dysautonomia (1,2). Anti-NMDAR encephalitis was initially described as paraneoplastic syndrome affecting young women with ovarian teratomas (3). Subsequently, it has been observed in patients of all ages and both sexes, with or without teratomas (1,4). The concept of disease was established with the identification of antibodies against NMDAR (2,5). Since then, the characteristic clinical features have been defined (1,2). However, impairment of visual function associated with anti-NMDAR encephalitis has not been well described. We present a case of anti-NMDAR encephalitis displaying transient symptoms of dyschromatopsia, prosopagnosia, partially impaired visual object recognition, and dysfunction of stereopsis during the recovery period.

CASE REPORT

A 20-year-old woman was admitted to hospital with generalized seizures that developed following headache, fever, memory disturbance, and psychosis. She had dyskinesia of her upper limbs, hypersialosis, and hypoventilation requiring sedation and intubation with ventilation. One month later, she was transferred to our institution. On admission, cerebrospinal fluid examination showed mild lymphocytic pleocytosis (11 cells mm⁻³) with a protein of 29 mg/dL (normal: 15–40 mg/dL), and a glucose of 74 mg/dL (normal: 50–70 mg/dL). Magnetic resonance imaging (MRI) of the brain only showed a small hyperintensity in the white matter close to the left insular gyrus (Fig. 1). Because the patient’s clinical course was highly suspicious for anti-NMDAR encephalitis, she underwent screening for an ovarian tumor and began on high-dose methylprednisolone (1000 mg/d for 3 days). Abdominopelvic MRI, computed tomography, and transrectal ultrasound revealed a mass in the left ovary and retroperitoneal space. Two weeks later, antibodies against GluN1/GluN2 heteromers of the NMDAR were detected in the patient’s serum and cerebrospinal fluid. No other anti–neuronal antibodies were found including anti-amphiphysin, anti-Yo, anti-Ri, anti-Hu, anti-Ma1, anti-Ma2 (Ta), or anti-recoverin.

The patient underwent removal of the ovarian and retroperitoneal tumors, which were, on pathological examination, mature cystic ovarian teratoma and retroperitoneal...
ganglioneuroma, respectively. In addition, she received immunotherapy comprising high-dose methylprednisolone (1000 mg/d for 3 days; 3 courses), intravenous immunoglobulin, and cyclophosphamide (750 mg/m²; 3 courses).

The patient’s consciousness gradually improved, and she was weaned off the ventilator 15 weeks after admission. Upon awakening, she reported lack of color sensation, inability to recognize faces, and impairment of object recognition and stereo perception. The frontal assessment battery (FAB) and revised Hasegawa dementia scale (HDS-R) were performed. She scored 16/18 on the FAB and 26/30 on the HDS-R (normal ≥21/30 points). She also took the visual perception test for agnosia (VPTA). In this test, a score of 0 indicates 100% correct answers and full points indicate 100% incorrect answers. A score of more than 50% indicates severe impairment of the function examined. The VPTA demonstrated severely impaired object recognition by sight (score 13/16 vs 4/16 for object recognition by touch) and face recognition (score 16/16 in both naming familiar persons from photographs and pointing at photographs of familiar persons. The VPTA also demonstrated mild or severe impairment reading “kana” or “kanji” characters (scores 4/12 and 8/12, respectively) and describing the topography of familiar surroundings (score 2/2). The results of the visual search (scores 1/20), solid line bisection (1/6), and judgment of line orientation (0/6) tasks in the VPTA ranged from normal to slightly abnormal.

Initial neuro-ophthalmic testing revealed visual acuity of 20/125, right eye, and 20/50, left eye. Pupillary reaction, extraocular movements, and anterior and posterior segment examination were normal. In evaluating color perception using the Farnsworth dichotomous test (Panel D-15), the patient could not arrange the color stimuli; all test stimuli were recognized in a monochromatic fashion in both eyes (Fig. 2A). She also demonstrated difficulty in recognizing familiar objects by visual inspection alone, such as pens.

FIG. 1. Brain magnetic resonance imaging includes noncontrast axial T1 (A), T2 (B), postcontrast T1 (C), and coronal fluid-attenuated inversion recovery (FLAIR) (D) images. An area of increased signal (arrows) is present on the T2 (B) and FLAIR (D) scans.
scissors, or bottles of eye drops. While follow-up brain MRI was unchanged, \(^{18}\text{F-fluoro-2-deoxy-d-glucose}\) (FDG) positron emission tomography (PET) revealed hypometabolism in both occipital lobes (Fig. 3).

Four weeks later, the patient’s visual acuity was 20/25, right eye, and 20/20, left eye. Panel D-15 testing revealed random crossing in both eyes (Fig. 2B). The patient lacked all stereo perception with the Titmus stereo test and was still unable to recognize faces (VPTA score 12/16), even her family members. Voice recognition allowed her to recognize her family and distinguish men from women. The patient demonstrated partially impaired visual object recognition (VPTA score 7/16), but could recognize an object correctly when holding it in her hands (VPTA score 1/16). Kinetic perimetry revealed small paracentral scotomas in each eye, and optical coherence tomography (3D-OCT 2000; Topcon Corp., Tokyo, Japan) revealed no abnormal findings of the macula or optic nerve. Fourteen weeks after her referral to our institution, the patient’s visual acuity was 20/20 in both eyes, and kinetic perimetry was normal. She could recognize colors, faces, and objects. Panel D-15 testing revealed a normal minor transpositional error in the right eye and normal perfect arrangement in the left eye (Fig. 2C). Titmus tests revealed that her stereo acuity had improved to 40 seconds of arc. VPTA results were in the normal range for object recognition, face recognition, reading, and describing topography. Over 1 year of follow-up, the patient has remained stable and brain MRI findings remained unchanged.

**FIG. 2.** Sequential results of Farnsworth dichotomous test (Panel D-15). A. Initially, this patient was unable to arrange the color stimuli in order. B. Four weeks later, the patient arranged the stimuli but random crossing occurred in both eyes. C. At 14 weeks, there are minor transpositional errors in the right eye with a perfect arrangement in the left eye.

**FIG. 3.** Positron emission tomography with \(^{18}\text{F-fluoro-2-deoxy-d-glucose}\) shows hypometabolism in the occipital cortex bilaterally on axial (A) and coronal (B) sections.
DISCUSSION

Anti-NMDAR encephalitis has characteristic clinical features of memory disturbance, psychiatric symptoms, seizures, involuntary movements, abnormal eye movements, central hypoventilation, and dysautonomia (1,2,6). Recent reports have suggested that the pathogenesis of anti-NMDAR encephalitis involves antibodies against the GluN1 subunit of the NMDAR, which deplete the NMDAR clusters on neurons, resulting in dysfunction of signal transmission mediated by glutamergic synapses (1,2,7–10). Involvement of cortical or subcortical structures is postulated to cause specific clinical symptoms: memory disturbances, psychiatric symptoms, and seizures are likely due to dysfunction in the cortical frontal and/or temporal lobes (1,2,11,12), and involuntary movements and central hypoventilation due to dysfunction in the subcortical structures of the basal ganglia or brainstem (3,13,14).

Our patient demonstrated a variety of visual impairments. Color sensation, face recognition, object recognition, and stereopsis are higher-order visual functions in which information is processed in distinct regions of occipital, occipitotemporal, and occipitoparietal cortices and segregated dorsal and ventral streams (15–19). Damage to these cortical visual processing regions causes specific clinical findings depending on which part of the cortex is involved (20,21). For example, loss of stereopsis is caused by bilateral occipitoparietal lesions (21), while prosopagnosia and cerebral dyschromatopsia are caused by bilateral lesions of the fusiform gyri (16,21). Our patient may have developed complex visual impairments due to prolonged dysfunction of signal transmission in occipitotemporal and occipitoparietal cortices. PET revealed hypometabolism in both occipital lobes, a pattern previously reported in anti-NMDAR encephalitis (22). We postulate that the hypometabolic regions included the fusiform gyri bilaterally contributing to our patient’s visual impairment. The white matter hyperintensity detected on MRI is unlikely a cause of visual dysfunction as it remained unchanged throughout the clinical course.

Krueit et al (23) described retrochiasmatic optic neuritis in a 15-year-old girl during a relapse of anti-NMDAR encephalitis. Because bilateral paracentral scotomas were observed on kinetic perimetry in our case, optic nerve involvement is conceivable. However, we did not detect a relative afferent pupillary defect, fundus changes, or signs of optic nerve abnormalities on MRI. The pattern of visual field loss is inconsistent with involvement of the lateral geniculate nucleus, which also appeared unremarkable on MRI. The cause of the visual impairments in our patient was ascribed to dysfunction of the cerebral visual system. The possibilities of anoxia and nonconvulsive seizures are unlikely because the patient had no episodes of severe hypoxemia, no cortical laminar necrosis or edema in the white matter on MRI, no epileptiform discharges on electroencephalography, and no focal hyper- or hypometabolism revealed by PET.

Tumor removal and immunotherapy are proposed treatments for anti-NMDAR encephalitis in patients with neoplastic disease (2,23). Early tumor removal results in a better clinical outcome (2,11), especially within 4 months of the appearance of neurological symptoms (1). In our case, removal of the ovarian teratoma and retroperitoneal ganglioneuroma was performed within 2 months of symptoms onset. In patients that lack response to first-line therapy or failure to detect a tumor, additional management options include rituximab (2,24,25).

ACKNOWLEDGMENTS

We thank Professor Josep Dalmau (Institució Catalana de Recerca i Studis Avançats (ICREA), Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Service of Neurology, Hospital Clinic, University of Barcelona and Department of Neurology, University of Pennsylvania) for analysis of the antibodies against NMDA receptor. We also thank Ms. S Umezaki (occupational therapist) for conducting repeated VPTA.

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Intermittent Horner Syndrome in a Pediatric Patient

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Abstract: Intermittent Horner syndrome is uncommon in both the adult and pediatric population. We describe a case of a pediatric patient with an intermittent Horner syndrome. Infrared photography and videography were used to help establish the diagnosis.

doi: 10.1097/WNO.0000000000000062
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A 14-year-old healthy boy was evaluated for a history of episodic right upper eyelid ptosis accompanied by miosis of the right pupil. His parents noted this on 4 occasions in the week preceding his office visit. Each episode lasted 15–20 minutes and resolved completely. There was no associated headache, rhinorrhea, tearing, nasal congestion or anhidrosis, nor a history of head or neck injury. Two weeks before presentation, the patient was struck in the right eye with a snowball. At that time, he did not seek medical attention. His mother reported some mild swelling of the right eyelids that resolved within 1 week.

Initial neuro-ophthalmic testing was unremarkable without ptosis or anisocoria. During the course of the examination, the patient developed a mild right upper lid ptosis and miosis of the right pupil (Fig. 1A). Infrared videography revealed right pupillary dilation lag (See Supplemental Digital Content 1, Video 1, http://links.lww.com/WNO/A88). The ptosis and miosis resolved after 20 minutes (Fig. 1B), as did the pupillary dilation lag (See Supplemental Digital Content 2, Video 2, http://links.lww.com/WNO/A89). The ocular and neurological examinations were otherwise normal, and no triggering maneuvers were identified.

Magnetic resonance imaging (MRI) and magnetic resonance angiography of the brain were unremarkable. MRI of the neck revealed a 1.7-cm cervical syrinx extending from C5 through C7, which spared the interomediolateral cell columns (Fig. 2A). MRI of the neck also revealed 2 nodules in the right portion of the thyroid gland. Thyroid ultrasound demonstrated 2 heterogeneous solid nodules, one measuring 0.8 cm × 0.9 cm × 2.0 cm in the right upper pole and the other measuring 0.6 cm × 0.8 cm × 0.9 cm in the right midpole. Neither nodule was in contact with the sympathetic chain. Thyroid function studies were normal, and ultrasound-guided needle biopsy of the thyroid nodules revealed...
no signs of malignancy. Three months after initial presentation, the patient reported less frequent episodes of ptosis and miosis that totally resolved 6 months after initial presentation.

Our patient’s findings are consistent with an intermittent Horner syndrome. The fluctuating clinical course is presumably caused by a reversible functional impairment of the oculosympathetic pathway to the right eye. Although intermittent Horner syndrome has been associated with cluster headaches and spinal cord lesions (1–4), the etiology in our patient is uncertain.

The presentation of Horner syndrome related to cluster headache is variable and, in some cases, its onset precedes the development of headache by several years (5,6). Other cases have been described in which patients experience no pain yet develop miosis, ptosis, and other accompanying symptoms without experiencing pain including rhinorrhea, nasal stuffiness, and lacrimation. This entity is known as cluster headache sine headache (6–8). Episodic Horner syndrome in the absence of headache, rhinorrhea, nasal stuffiness, and lacrimation also has been reported (3). This case was suspected to be a cluster headache variant (3).

Another consideration for the intermittent Horner syndrome observed in our case is the patient’s history of ipsilateral ocular trauma. The Horner syndrome began 2 weeks after the trauma and resolved after 6 months. However, the ocular injury could have theoretically resulted in neck and vascular damage that led to the development of the ipsilateral intermittent Horner syndrome. However, no structural damage was detected by neuroimaging studies.

Thyroid pathology has been associated with Horner syndrome when the cervical sympathetic pathway is affected (9). However, ultrasound revealed that the thyroid nodules in our patient did not compress the sympathetic chain.

Syrinx of the cervical spinal cord may be a cause of Horner syndrome. This is because of dysfunction of the second-order neurons in the interomediolateral cell column in the C8 to T2 levels (10,11). Intermittent dysfunction of the oculosympathetic pathway has been reported from an acquired syrinx (12). The syrinx in our patient appeared centrally located in the cervical cord. Yet, it had a similar appearance to the syrinx reported by Pomeranz (11), in a patient who developed a right Horner syndrome. Fluctuations in the size of the syrinx or shifting fluid within it may have caused the intermittent Horner syndrome in our patient.

REFERENCES

Posterior Ischemic Optic Neuropathy in the Setting of Posterior Reversible Encephalopathy Syndrome and Hypertensive Emergency

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Abstract: We present the magnetic resonance imaging findings of posterior ischemic optic neuropathy in a patient with posterior reversible encephalopathy syndrome secondary to hypertensive emergency.

Journal of Neuro-Ophthalmology 2014;34:151–152
doi: 10.1097/WNO.0000000000000108

A 34-year-old woman came to the emergency department because of headaches and transient visual obscurations. The transient visual obscurations began 1 month before presentation and the headaches began 8 days previously. She had a history of untreated hypertension and migraine headaches. Visual acuity was 20/50 in the right eye and 20/400 in the left eye. A 1.2 log-unit left relative afferent pupillary defect was present. Visual fields to confrontation were full in the right eye and there was inferior constriction in the left eye. External and anterior segment examinations and intraocular pressures were normal in both eyes. There was bilateral optic disc edema with surrounding cotton wool spots as well as cotton wool spots, exudates, dot-and-blot, and flame hemorrhages in both maculae.

Neurologic examination was normal, but the patient’s blood pressure was 238/172 mm Hg. Computed tomography of the brain without contrast showed diffuse cerebral edema with transtentorial and tonsillar herniation. Serum creatinine was 1.48 mg/dL (normal: 0.57–1.11 mg/dL) consistent with acute renal injury. In the presence of acute end-organ damage with retinopathy, nephropathy, and central nervous system involvement on neuroimaging, she was diagnosed with hypertensive emergency.

Initial magnetic resonance imaging (MRI) of the brain, performed without contrast, showed extensive T2 and fluid-attenuated inversion recovery (FLAIR) abnormalities and diffusion restriction throughout the white matter of both cerebral and cerebellar hemisphere and the pons. There also were findings of increased intracranial pressure with diffuse loss of sulcation, cerebellar tonsillar herniation to 11 mm below the foramen magnum, posterior flattening of the globes, and intraocular protrusion of the optic discs (Fig. 1). The differential diagnosis for this constellation of imaging findings included hypoxic–ischemic encephalopathy, atypical posterior reversible encephalopathy syndrome (PRES), metabolic derangement, toxic exposure, acute disseminated encephalomyelitis, or atypical demyelinating disease.

FIG. 1. Initial magnetic resonance imaging. A. Sagittal fluid-attenuated inversion recovery image demonstrates signal abnormality in the pons (arrowhead) and cerebellar tonsillar herniation (arrow). B. Axial T2 scan shows posterior globe flattening and elevation of the optic discs (arrows).
The patient was admitted to the neurocritical care service and underwent treatment for systemic hypertension and placement of an external ventricular drain. Intracranial pressure was not measured.

Evaluation of demyelinating and autoimmune disease was negative. Repeat MRI of the brain without contrast 6 days after presentation demonstrated marked improvement in the degree of white matter abnormalities both supra- and intratentorially, most consistent with PRES. On T2 imaging, there was increased signal in the intraorbital segment of the left optic nerve anterior to the optic canal (Fig. 2A). Diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADC) sequences map demonstrated restricted diffusion (Fig. 2B, C). These imaging findings were felt to be most consistent with an acute left posterior ischemic optic neuropathy.

After 3 weeks of treatment for hypertension, the patient’s visual acuity was 20/20 in the right eye and 20/30 in the left eye. There was a left relative pupillary defect, but optic disc edema and hypertensive retinopathy were resolving. Two months after discharge, follow-up imaging showed complete resolution of the T2 and FLAIR white matter abnormalities and resolution of the T2 and DWI optic nerve abnormalities of the left optic nerves.

Sadda et al (1) summarized the clinical settings for the occurrence of posterior ischemic optic neuropathy to include:

1. The perioperative period following a variety of surgical procedures felt to be secondary to anemia from excessive blood loss and associated hypovolemic hypotension
2. Giant cell (temporal) arteritis causing inflammatory narrowing of the vasculature of the optic nerve, resulting in ischemic injury
3. Non-arteritic atherosclerotic vascular disease secondary to the systemic risk factors of hypertension, diabetes mellitus, hypercholesterolemia, cardiac disease, and cerebrovascular disease.

In addition to these clinical settings, there are reports of PION associated with use of sildenafil (2), and Wegener disease (3). The imaging findings in PION have been previously documented, and include restricted diffusion on DWI similar to our case (4–7). Neuroimaging abnormalities in patients with PRES are typically distributed in the parieto-occipital regions followed by the frontal lobes, inferior temporo-occipital junctions, and cerebellum. Atypical cases involve the deep white matter and brainstem and rarely demonstrate diffusion restriction or findings of elevated intracranial pressure. While our patient did have imaging findings atypical for PRES, her presentation, clinical course, and response to treatment were consistent with this diagnosis.

REFERENCES
Accessory Lateral Rectus in a Patient With Normal Ocular Motor Control

Yaping Joyce Liao, MD, PhD, Jaclyn J. Hwang

Abstract: Although supernumerary extraocular muscles are common in monkeys and other species, they are relatively rare in humans and typically are noted in the context of childhood strabismus. We present a case of an incidentally found unilateral accessory lateral rectus muscle in a 51-year-old woman with normal ocular motor control. In this patient, the accessory lateral rectus was approximately 10% the size of a normally sized lateral rectus muscle. It originated from the orbital apex, traveled between the optic nerve and the lateral rectus and attached to the superolateral aspect of the globe. This unique case demonstrates that accessory lateral rectus in humans may have no impact on eye movement and ocular alignment.

doi: 10.1097/WNO.0000000000000109

A 51-year-old woman with a pituitary tumor was referred for evaluation of visual function. She had no subjective vision complaints. Visual acuity was 20/20 in both eyes, with no relative afferent pupillary defect, normal color vision, and normal visual fields. Her anterior and posterior segment examinations were unremarkable, and ductions, saccades, pursuit, and ocular alignment in all directions of gaze were normal.

Brain magnetic resonance imaging (MRI) revealed slight pituitary enlargement without optic chiasm compression. In the orbit, there was a small, linear structure located parallel and just medial to the right lateral rectus. It arose as a discrete entity from the orbital apex and attached to the globe superiorly and medially to the lateral rectus. It had the same signal intensity in all sequences as that of the other extraocular muscles. It was not consistent with a vascular structure, fibrous band, or tumor, but rather appeared as an accessory lateral rectus muscle (Fig. 1). We estimated the size of the accessory lateral rectus muscle using thresholding and quantification of the coronal MRI images with ImageJ (http://rsb.info.nih.gov/ij/), and it measured 11.3% that of the right and 11.7% that of the left lateral rectus muscles (1). Ultrasound was not performed to confirm whether it contracted like a muscle.

Accessory lateral rectus muscle in humans is relatively rare and typically discovered when associated with childhood strabismus (2–5). It has been reported in one case of congenital third nerve palsy (2) and in a patient with orbital malformation syndrome (6). As in other patients evaluated with CT (2,6,7) and MRI (3,8,9), the accessory lateral rectus in our patient appeared to run parallel and just medial to the normally sized lateral rectus but was much smaller in size (6,8,9).
Human pathologic studies have shown that an accessory rectus muscle can originate discretely or in the same tendon as that of the lateral rectus. It may have a muscle belly or exist simply as a fibrous band. It can divide anteriorly and join different rectus muscles, not necessarily causing strabismus (3,9,10). The majority of cases of accessory lateral rectus are unilateral (8). There is 1 reported case of bilateral, asymmetric accessory lateral rectus muscles in a patient with Gorlin syndrome, a condition attributed to Pch 1 mutation and disruption of sonic hedgehog signaling (6).

Although supernumerary extraocular muscles have been associated with strabismus, our case provides evidence that the presence of accessory lateral rectus muscle does not necessarily impair ocular motility. Supernumerary extraocular muscles should be considered in cases of unusual strabismus patterns (5,9) or when strabismus surgery does not achieve the expected result, because release of accessory muscle is sometimes necessary as part of the surgical procedure (2,6,7,11,12). Intraoperative forced duction testing should be performed to ensure that no other unsuspected anomalies or muscles are present.

Although accessory lateral rectus is relatively rare in humans, it is a normal finding in monkeys. It is typically very small, inconsistently located, often superior to the optic nerve and medial to the lateral rectus (13,14). In monkeys, the accessory lateral rectus has been attributed to a developmental remnant of the retractor bulbi, which is innervated primarily by the sixth nerve but may also be innervated by the third nerve. Although the function of the accessory lateral rectus is unclear, it is not usually associated with strabismus in monkeys (13), and, in fact, it has been proposed to be protective against esodeviation, which is rare in monkeys (14,15). Similarly in amphibians, the accessory lateral rectus is thought to protect the eye and to prevent ocular protrusion (10).

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Optic Chiasm Involvement on MRI With Ethambutol-Induced Bitemporal Hemianopia

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Abstract: While ethambutol optic neuropathy usually causes central or cecocentral scotomas, bitemporal visual field defects also have been reported. The pathogenesis of the bitemporal hemianopia has not been established. This article describes magnetic resonance imaging abnormalities involving the optic chiasm in a patient with bitemporal visual field loss. To our knowledge, these neuroimaging findings have not been previously described in association with ethambutol therapy.

doi: 10.1097/WNO.0000000000000095

Ethambutol is a bacteriostatic antimicrobial agent used in the treatment of mycobacterial infections. Ethambutol optic neuropathy is a complication arising from its use; it is dose dependent and usually reversible (1). Optic neuropathy commencing as early as 3 days after ethambutol therapy has been documented (2,3). Visual field changes in ethambutol optic neuropathy vary from central, cecocentral, bitemporal field defects and peripheral constriction. In previous reports of 26 patients with ethambutol-induced bitemporal visual field defects, neuroimaging had been normal (2,4–7). We present optic chiasm involvement on magnetic resonance imaging (MRI) in a patient with ethambutol-induced bitemporal hemianopia.

CASE REPORT

A 72-year-old woman weighing 70 kg reported progressive blurring of vision in both eyes 4 months after commencing medications for atypical mycobacterial infection. She had been evaluated for multiple pulmonary nodules. Percutaneous biopsy of a lung lesion showed granulomatous inflammation containing multiple acid-fast organisms. Amplified *Mycobacterium tuberculosis* direct test was negative as was examination of hypertonic saline-induced sputum smear and culture for *tuberculosis*. Mantoux test also was negative. Atypical mycobacterial infection, especially *Mycobacterium avium* complex, was considered likely by her infectious diseases specialist. The patient was concurrently worked up for a renal mass, which potentially would require chemotherapy. Since chemotherapy is contraindicated in active pulmonary tuberculosis, there was urgency to initiate treatment for her pulmonary condition.

The patient was aggressively treated for pulmonary atypical mycobacterial infection and empirically for possible pulmonary tuberculosis. She was prescribed 1600 mg of ethambutol daily (23 mg/kg) for 2 months followed by 1300 mg daily (19 mg/kg/d), 300 mg of isoniazid, 600 mg of rifampin, 250 mg of azithromycin, and 25 mg of vitamin B6 (pyridoxine). All anti-tubercular medications were stopped immediately after she reported blurred vision.

Additional medications included aspirin, amlodipine, atorvastatin, ramipril, metoprolol, hydrochlorothiazide, and inhalers of tiotropium bromide, budesonide and formeterol, and albuterol. Comorbidities included chronic obstructive pulmonary disease, hypertension, and hypercholesterolemia.

On examination, visual acuity was 20/200 bilaterally and the patient could identify only 1 of 17 Ishihara color plates with each eye. Pupils were equal and sluggishly reactive to light, with no relative afferent papillary defect. Ocular motility and fundoscopy were normal. Automated perimetry revealed bitemporal visual field defects (Fig. 1A).
Brain MRI showed increased signal within the optic chiasm (Fig. 2A, B), and diffusion-weighted imaging showed no evidence of restricted diffusion (Fig. 2C).

Complete blood count, erythrocyte sedimentation rate, antinuclear antibody, anti-neutrophil cytoplasmic antibodies, and serum vitamin B12 were normal. Screening for syphilis, human immunodeficiency virus, varicella zoster, and herpes simplex virus antibodies was negative. Cerebrospinal fluid analysis was normal. Renal function tests were normal with creatinine and urea values of 56 μmol/L.

**FIG. 1.** Automated visual fields (24-2 Humphrey). A. Bitemporal hemianopia is present 4 months after commencing ethambutol. B. Improvement in visual fields 16 weeks after discontinuing ethambutol.

**FIG. 2.** Brain magnetic resonance imaging. A. Coronal T2 image shows hyperintense signal within the optic chiasm. B. Axial T2 image demonstrates a small amount of hyperintensity within the optic chiasm anterior to the infundibulum, while the more posterior hyperintensity is likely volume averaging artifact associated with cerebrospinal fluid (CSF). C. Axial diffusion-weighted image shows no evidence of restricted diffusion. D. Sixteen weeks after ethambutol was stopped, axial T2 scan reveals normalization of the signal intensity within the optic chiasm. The subtle hyperintensity in the superior aspect of the optic chiasm may represent gliosis or volume averaging from adjacent CSF signal.
DISCUSSION

Bitemporal hemianopic visual field defects in ethambutol toxicity implicate a lesion in the optic chiasm, but neuroimaging abnormalities of the chiasm have not been reported previously among 26 patients with this pattern of field loss (2–6). Our patient had bitemporal hemianopia with a T2 hypointense signal in the optic chiasm on MRI. Ethambutol-treated animals have shown pathologic changes within the central nervous system with susceptibility of the optic nerves, chiasm, and tracts (7–9). In the rat model, bilateral involvement of the optic chiasm (affecting both crossed and uncrossed fibers) and the intracranial portions of the optic nerves with axonal swelling and thinning of the myelin sheaths without demyelination have been reported (7). In this study, the optic nerve head as well as the intraorbital optic nerve and the retina were reported to be spared. Kinoshita et al (9) observed microglial proliferation and demyelination within the optic nerves, chiasm, and tracts in ethambutol-treated monkeys. In 1 of the 3 monkeys, demyelination was seen at the center of the optic chiasm. Schmidt (8), in a study of rhesus monkeys treated with high doses of ethambutol, noted degenerative changes, including glial reaction, vacuolation, and demyelination at the center of the optic chiasm as well as in the proximal optic tracts and distal optic nerves. These degenerative changes occurred at doses of ethambutol much higher than therapeutic doses in man. It may follow that at lower doses in humans, the pathologic changes, if detected early, may be reversible or not progressive.

There is also evidence that ethambutol is toxic to the retina, particularly retinal ganglion cells (10). Necrosis of retinal ganglion cells and a decrease in their numbers in the parafoveal area (especially nasally) have been documented. Glial reaction may occur in the retinal nerve fiber layer, with sparing of other portions of the retina. In humans, electrophysiologic studies, including the electro-oculography and multifocal electrotetrograming (mfERG), have demonstrated dysfunction of other layers of the retina apart from the retinal ganglion cells, including the retinal pigment epithelium, photoreceptors, and bipolar cells in the macula (4,11–14). Liu et al (4) studied 2 patients treated with ethambutol with bitemporal visual field defects and found the area of abnormal mfERG corresponded with the areas of bitemporal visual field loss. Orbital and brain MRI were normal, and it was concluded that ethambutol-induced bitemporal field may result, at least in part, from retinal toxicity.

Various cellular mechanisms have been hypothesized in ethambutol-induced cytotoxicity. One study reported that ethambutol may cause death of retinal ganglion cells by acting as a chelating agent that depletes copper and zinc (15). Heng et al (10) concluded that ethambutol can cause mitochondrial dysfunction in the retinal ganglion cells via glutamate excitotoxicity. Contrary to these theories, Yoon et al (16) proposed that retinal ganglion cell damage caused by ethambutol is neither due to the depletion of zinc nor glutamate excitotoxicity, but through another mechanism that requires intracellular zinc.

Our patient was treated with 2 other medications that may have affected her vision, azithromycin and isoniazid. Unlike most other macrolides, azithromycin generally does not interact with other medications causing adverse effects. This may be due to the fact that this antibiotic does not induce and bind to hepatic cytochrome P450 IIIA isoenzyme system (17).

Optic neuropathy has been described in patients treated with ethambutol in combination with isoniazid (18,19). In one report, there was minimal change in visual function after discontinuing ethambutol, but significant improvement after stopping isoniazid (18). There may be an additive toxic effect when isoniazid is used in combination with ethambutol and it is recommended to stop both medications as soon as the patient develops visual impairment (19).

Our case illustrates clinical–neuroimaging correlation of optic chiasmal involvement from ethambutol toxicity. We await additional studies using high-resolution MRI of the anterior visual pathways to confirm our findings.

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Geotropic Central Paroxysmal Positional Nystagmus in a Patient With Human Immunodeficiency Virus Encephalopathy

Tae-Ho Yang, MD, Sun-Young Oh, MD, PhD

Abstract: Central vestibular lesions may cause paroxysmal positional nystagmus (PPN) or paroxysmal positional vertigo as a result of lesions involving the brainstem dorsolateral to the fourth ventricle or the cerebellar nodulus/uvular region. PPN usually presents as persistent downbeating nystagmus during head hanging or as apogeotropic horizontal nystagmus during head turning in the supine position. Geotropic PPN during head turning in the supine position has not been previously reported. We report such a case in a patient with HIV encephalopathy.

Journal of Neuro-Ophthalmology 2014;34:159-161
doi: 10.1097/WNO.0000000000000094
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Pathological nystagmus and vertigo during head positioning usually are caused by a peripheral vestibular disorder, such as benign paroxysmal positional vertigo (BPPV) (1). Central lesions, which may cause paroxysmal positional nystagmus (PPN) or paroxysmal positional vertigo (PPV), may be the result of a variety of disorders involving the cerebellar nodules/uvula or the region dorsolateral to the fourth ventricle (1–3). Most often PPV and PPN present as persistent downbeating nystagmus in the head-hanging position or pure torsional or horizontal nystagmus (2–4). While apogeotropic PPN has been described (3–5), we are unaware of published reports of geotropic PPN. We present a case of geotropic PPN in a patient with HIV encephalopathy.

CASE REPORT

A previously healthy 54-year-old man presented with acute vertigo and imbalance, nausea, vomiting, and drowsiness of several weeks in duration. His medical history was unremarkable, except for a recent history of persistent cough and myalgias. Examination showed no spontaneous nystagmus but gaze-evoked nystagmus (GEN) with lateral gaze. Positional tests revealed geotropic horizontal nystagmus during lateral head turning in the supine position. The patient had mild dysmetria and intention tremor bilaterally as well as severe ataxia. The remainder of the neurological examination was unremarkable.

Video-oculographic recording (0.1° resolution, 60 Hz sampling rate; SMI, Teltow, Germany) showed horizontal GEN (Fig. 1A) and direction-changing, geotropic, horizontal nystagmus on lateral head turning in the supine position, with left-beating nystagmus more intense than the right beating (Fig. 1B) (see Video, Supplemental Digital Content, http://links.lww.com/WNO/A92). Subtle down-beat nystagmus also was observed during head hanging and the Dix-Hallpike test in either direction. The patient had saccadic hypometria and impaired smooth pursuit gain in both horizontal directions. Bithermal caloric tests, ocular and cervical vestibular-evoked myogenic potentials, brainstem auditory-evoked potentials, and subjective visual vertical test were normal.

Magnetic resonance imaging of the brain showed diffuse periventricular white matter changes without brainstem or cerebellar abnormalities. Cerebrospinal fluid findings were normal. Chest computed tomography revealed right upper and middle lobe consolidation that was proven to be cryptococcal and Pneumocystis carinii pneumonia on biopsy. Serum HIV antibody was positive on enzyme-linked
Central positional nystagmus usually manifests as downbeating in the head-hanging position (6), or upbeating in the supine position, or torsional nystagmus (7,8). Horizontal positional nystagmus caused by central pathology, such as infarction of the cerebellar nodules usually is apogeotropic (3,5,9,10). Most often, accompanying cerebellar and ocular motor findings allow the clinician to distinguish central from BPPV. However, at times, this may prove difficult because the 2 syndromes may present as isolated positional vertigo and nystagmus without other neurological deficits.

In our patient, the acute onset of positional vertigo and direction-changing, persistent, geotropic positional nystagmus with the supine roll test without lying-down or head-bending nystagmus may have led to the diagnosis of geotropic type of horizontal canal (HC)-BPPV. However, the patient also showed horizontal GEN, severe ataxia, and bilateral dysmetria. Moreover, the geotropic positional nystagmus and vertigo persisted even after repeated repositioning maneuvers for geotropic HC-BPPV.

GEN is a characteristic sign of impaired gaze-holding and neural integration, and it is usually caused by cerebellar disorders that involve the vestibulocerebellum or by brainstem lesions affecting the nucleus prepositus hypoglossi and medial vestibular nucleus or their connections (11,12). Apogeotropic central positional nystagmus is caused by lesions involving the cerebellar nodulus (3,4,13), which has connections with the otolith organs and the semicircular canals and controls otothluc-ocular reflexes and otolithic modulation of the canal-ocular reflexes. Although the mechanism is unknown, direct or indirect injuries because of HIV infection may damage the otolith, vestibular nuclei, or cerebellum. The change in the graviceptive (otolithic) input induced by positional changes may be the precipitating factor for central PPN, and inactivation or stimulation of these pathways may induce nystagmus that is influenced by the position of the head.

HIV/AIDS–associated vestibular dysfunction may be caused by direct effects of the virus on the peripheral and central vestibular system, together with HIV/AIDS–associated opportunistic infections, including otoophylis, encephalitis, and cochleovestibular neuropathy (14). Previous autopsy findings in HIV patients have revealed subacute encephalitis with diffuse damage to the cortex, cerebellum, and brainstem, with myelinic degeneration (15). Vestibular dysfunctions were evident at all disease stages, even in asymptomatic individuals without reported neurological or vestibular symptoms. Central vestibular involvements were noted in more than 50% of asymptomatic HIV-positive adults (8), and eye movement disorders, including nystagmus, were present in more than a half of the patients (14). However, to date, there has been no report of geotropic PPN as an early manifestation of HIV-related, central vestibular neurological syndrome PPN.

REFERENCES


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**Ode to Neuro-Ophthalmology**

Smita Praveen, MBBS, MS
Chennai, India

Neuroscience is a subject that’s first rate
Isn’t it amazing the way neurons communicate?
From crying to laughing
And reading to writing
It’s the brain that rules—no debate!
Neuro-ophthalmology is that branch of medical science
That deals with problems of our visual appliance
It requires eliciting a good history
To solve the patient’s vision loss mystery
Here neurology, radiology and ophthalmology have a holy alliance!
Now, the optic nerve could be swollen or pale
To decipher the cause I need to go into great detail
Is it MS, diabetes or simply a fall
That could be the culprit behind it all?
It gives me closure when the true reason I can unveil!
When there’s headache and weight gain and seeing double
It could spell major trouble
Is the CSF pressure sky high?
Is my diet of burgers and fries the bad guy?
IIH snaps me out of the fast food bubble!
A dysfunctional pupil can result in glare
While thyroid disease may leave me with an unsightly stare
Tumors and strokes can affect my field of vision
Neuro-imaging aids here in making my decision
Enabling me to treat the condition with due care.
Sometimes when the eyeballs oscillate
There are some questions that I must postulate
Do the eyes shake up or down or sideways
Is it recent or has it been around always
To treat nystagmus one must be a doctor consummate!
The major challenge for our generation
Is to beat the rapid rate of axonal degeneration
Tremors and weakness and memory loss
Are sufficient to make one quite cross
The need of the hour is neuronal regeneration!
The last decade was dedicated to studying human genes.
But this one is all about brain proteins
Neuro-ophthalmology is right up there
At the cutting edge of revolutionary healthcare
The future belongs to neuroscience and its allied themes!
Positional Suppression of Periodic Alternating Nystagmus

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Abstract: A 43-year-old man with a high-grade glioma involving the cerebellar nodulus showed a near-complete suppression of periodic alternating nystagmus (PAN) in the lateral decubitus position to either side. This positional modulation of PAN is consistent with suppression of the velocity storage mechanism by head position changes (tilt dumping) and is supportive of the role of the velocity storage mechanism in generating PAN.

doi: 10.1097/WNO.0000000000000098

Periodic alternating nystagmus (PAN) is characterized by a horizontal jerk nystagmus, which reverses its direction periodically with a brief transition period (1). Although the pathogenesis of PAN remains uncertain, it has been ascribed to the instability of the velocity storage mechanism because of lesions involving the cerebellar nodulus or its connections with the vestibular nuclei and related structures (2). Because the velocity storage mechanism is suppressed by head position changes in the direction of gravity (tilt dumping) (3), positional changes may affect PAN by altering the graviceptive inputs to the nodulus.

CASE REPORT

A 43-year-old man was referred for evaluation of dizziness and imbalance for 3 months. Examination showed spontaneous horizontal nystagmus that changed directions approximately every 2 minutes with a brief transition period for several seconds. Downbeat nystagmus became evident during the transition period (See Supplemental Digital Content, Video 1, http://links.lww.com/WNO/A93). While looking straight ahead in the sitting position, 1 cycle of PAN consisted of alternating left- and right-beating nystagmus with each half-cycle lasting approximately 110 seconds and an intervening transition period of approximately 15 seconds (Fig. 1A; See Supplemental Digital Content, Video 1, http://links.lww.com/WNO/A93). During each half-cycle, the nystagmus gradually built up and then decreased with a maximum slow phase velocity reaching approximately 7°/s in either direction (Fig. 1A). Horizontal head shaking, head impulses, and vibratory stimulation on the brow or the mastoids did not affect the intensity or periodicity of the PAN. The patient underwent various positional changes including head tilt to either side, head bending while sitting, lying on his back, lying on his face, and lying on either side. The PAN dissipated over about 2 cycles while lying on either side, regardless of the initial direction of nystagmus (Fig. 1B; See Supplemental Digital Content, Video 2, http://links.lww.com/WNO/A94). In contrast, the basic pattern of PAN was maintained in other positions although the periodicity or the intensity of PAN was slightly affected (Fig. 1A). Head impulse vestibulo-ocular reflex, bithermal caloric tests, fundus photography, ocular vestibular evoked myogenic potentials (VEMP), and pure tone audiogram were normal.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the full text and PDF versions of this article on the journal’s Web site (www.jneuro-ophthalmology.com).

Supported by a grant of the Korea Health 21 R&D Project, Ministry of Health & Welfare, Republic of Korea (A080750).

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Brain magnetic resonance imaging (MRI) revealed enhancement around the anteroinferior cerebellum including the nodulus and flocculus (Fig. 1C), in the right medial temporal and suprasellar areas, and perimesencephalic cistern and internal auditory canals. Brain positron emission tomography (PET) showed hypermetabolism in the corresponding regions (Fig. 1D). The patient underwent right temporal lobectomy, and the pathology was consistent with a high-grade glioma.

DISCUSSION

PAN has been ascribed to nodular lesions and resulting disinhibition of the velocity storage mechanism that normally enhances the vestibular responses during lower-frequency stimulation (4,5). The nodulus has connections with the vestibular nuclei that take part in the velocity storage mechanism (6,7). Thus, spontaneous nystagmus augmented by increased vestibular storage activities would reverse the direction periodically because of a normal vestibular repair.
mechanism (8). In our patient, the enhancing MRI lesions and PET hypermetabolism in the area of the nodulus also support the nodulus as the neural substrate of PAN.

The nodulus is known to play an important role in the processing of otolithic signals through its connection with the otolithic organs, and it gives rise to positional nystagmus when damaged (8). Previously, apogeotropic positional nystagmus was induced during head turning in patients with nodular lesions while in the supine position (9). Accordingly, the role of apogeotropic positional nystagmus may be considered in the positional modulation of PAN in our patient. However, the suppression of both half-cycles of PAN and eventual resolution of the nystagmus during side-lying to either side do not support the role of apogeotropic positional nystagmus. Otherwise, the otolithic signal generated during the side-lying may have modulated the activity of the velocity storage mechanism. Indeed, the time constant of the postrotatory nystagmus is shortened when the head is tilted or bent down at the onset of postrotatory nystagmus, and this tilt suppression (dumping) is diminished in nodular lesions (3). The nodular dysfunction should have been partial in our patient to explain the positional modulation of PAN. It is unknown why the positional effect was greatest when the patient assumed a side-lying position. Because the direction of the PAN was horizontal, the possible effect of the gravity on PAN would have been maximal when it was mostly aligned with the interaural axis. The positional modulation of PAN in our patient differs from the findings of Furman et al (2) who showed no significant modulation with changes in static head position in 4 patients with PAN. The reason for this discrepancy is unclear. The completeness of nodular dysfunction or contribution of other cerebellar structures may be considered because the patients in the previous study (2) had diffuse cerebellar pathology. Another explanation may be peripheral vestibular involvement from leptomeningeal seeding around the brainstem and internal auditory canals as demonstrated on MRI. This may have altered the otolithic signals although this seems unlikely given the normal results of head impulse and caloric testing, ocular VEMP, and audiometry.

In conclusion, the positional modulation of PAN in our patient is consistent with suppression of the velocity storage mechanism by head position changes and is supportive of the role of the velocity storage mechanism in generating PAN.

REFERENCES
Sequential Episodes of Perioperative Ischemic Optic Neuropathy After Hip Surgery

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Abstract: Perioperative ischemic optic neuropathy (ION) after nonocular surgery is a rare complication leading to permanent and often severe vision loss. Due in part to the low prevalence of this complication, there remains no reliable way to predict which patients will develop ION. We present a patient with sequential episodes of unilateral perioperative ION, both occurring after otherwise uncomplicated hip operations. Patients and physicians should be aware that perioperative ION after one surgery may increase the risk of ION after subsequent surgeries.

doi: 10.1097/WNO.0000000000000093

Perioperative vision loss is a rare surgical complication most commonly due to ischemic optic neuropathy (ION). Perioperative anterior ischemic optic neuropathy (AION) most commonly occurs after cardiac procedures and is thought to arise from hypoperfusion of the posterior ciliary arteries supplying the optic nerve head (2). Previously reported cases of perioperative AION document acute unilateral or bilateral eye involvement after a single surgical procedure (2–4). Our patient experienced sequential episodes of perioperative ischemic optic neuropathy (ION) in each eye after otherwise uncomplicated hip operations.

CASE REPORT

A 50-year-old man, known to have tested positively for HIV, developed vision loss in the right eye after hip surgery. Three days previously, he underwent a total left hip explantation with debridement of an infected prosthetic hip. Two days later, he had repeat debridement of the left hip with placement of an antibiotic spacer. After the second operation, he noted sudden onset of painless vision loss in the superior visual field of the right eye.

On examination, visual acuity was 20/50, right eye and 20/30, left eye. Confrontation visual fields showed a superior visual field defect in the right eye and a right relative afferent pupillary defect (RAPD). Funduscopic examination revealed right optic disc edema and superotemporal pallor of the left disc (Fig. 1). No evidence of HIV retinopathy was present in either eye.

Noncontrast orbital computed tomography was normal. Two days later, vision in the right eye decreased to no light perception with increased optic nerve swelling. The patient was discharged home with a diagnosis of perioperative right AION.

Both surgical procedures preceding vision loss were performed in the lateral decubitus position. The first lasted approximately 4.25 hours with an estimated blood loss (EBL) of 3,200 mL. The patient received 3,700 mL crystalloid, 1,000 mL colloid, and 4 units of packed red blood cells (PRBCs). The second procedure lasted 4 hours, EBL was 400 mL, and the patient received 2,700 mL crystalloid, no colloid, and 2 units of PRBCs. Mean arterial pressure (MAP) remained between 55 and 90 mm Hg throughout both surgeries. Hematocrit was 41.1%, 31.9%, and 27.2% before the first surgery, after the first surgery, and after the second surgery, respectively. The corresponding hemoglobin levels were 13.3 g/dL, 10.6 g/dL, and 9.1 g/dL, respectively.

The patient had a history of bilateral hip replacements for avascular necrosis 4 years ago with multiple revisions and debridements of the left hip since that time. Two years previously, the patient experienced acute painless vision loss.

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The authors report no conflicts of interest.

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in the left eye after a left hip reimplantation. At that time, the patient reported a left inferior visual field defect 1 week after surgery, but there was no documentation of an ophthalmic examination. At that time, surgery was reported to be uncomplicated, lasting 3.5 hours, EBL of 500 mL, and administration of 5,000 mL of crystalloid. MAP remained between 60 and 100 mm Hg.

HIV was detected in the patient 17 years ago and was well controlled on highly active antiretroviral therapy (emtricitabine, tenofovir, and efavirenz) with a recent CD4 count of 529/µL and an undetectable viral load. He had been on the same antiviral regimen for at least 2.5 years.

One month after his most recent perioperative vision loss, visual acuity in the right eye was light perception. The right optic disc edema had resolved with development of optic disc pallor. The left eye examination remained unchanged, and left visual field testing showed an inferior altitudinal defect (Fig. 2).

**DISCUSSION**

Perioperative vision loss has been defined as occurring within 1 week of a surgical procedure (1,5). The differential diagnosis for perioperative vision loss, along with distinguishing clinical
features of each diagnosis, is shown in Table 1. Ischemic optic neuropathy, either anterior or posterior, is the most common cause of permanent perioperative vision loss. Our patient’s history of acute, painless perioperative vision loss in the left eye followed by superior segment optic pallor and an inferior altitudinal visual field defect in a “crowded” optic nerve is highly suggestive of previous perioperative AION. However, without documentation of the optic nerve appearance immediately after vision loss, posterior ischemic optic neuropathy (PION) remains a possibility. His most recent episode of vision loss is classic for perioperative AION: sudden painless decline in vision with a RAPD and optic disc edema within days of a surgical procedure.

Our patient was not on any medications that may have predisposed him to ION. Although anti-HIV nucleoside analogs such as emtricitabine have been implicated as potential triggers for vision loss in Leber hereditary optic neuropathy (LHON) by inhibiting mitochondrial enzymes (6,7), our patient had no family history of eye disease and the clinical presentation was not suggestive of LHON.

Estimates of perioperative ION range from 0.0004% for noncardiac surgeries (8) to 0.12% for spinal surgeries (9), with one study reporting an incidence of 0.013% for all nonocular surgeries performed at a single institution (1). Orthopedic surgeries tend to have a relatively low incidence of ION. Shen et al (10) reported a prevalence of 0.004% after hip surgery. Perioperative AION is most commonly associated with cardiac surgery, although cases have been reported after prostatectomy, liposuction, major vascular surgery (2–4), as well as after hip surgery and other orthopedic procedures (11,12). PION occurs most commonly after spinal surgeries, but also has been reported after radical neck dissections and cardiac surgery (2). The degree of vision loss in both AION and PION can range from mild visual field defects to no light perception (13,14). In one study of postoperative vision loss after spine surgery, 42% of patients with AION and 61% of patients with PION had no light perception (15). Although PION commonly presents with vision loss immediately after surgery, patients who develop AION often report normal vision for several days followed by rapid loss (13).

Various risk factors may contribute to perioperative ION and can be categorized as intraoperative hemodynamic, intraocular anatomic, and vasculopathic. Intraoperative risk factors include hypotension and anemia resulting from blood loss and volume replacement (14,16–18). Lee et al (15) found that 94% of ION cases after spine surgery had an anesthetic duration of 6 hours or more and 82% of cases had an EBL of 1 liter or more (15). Other proposed intraoperative risk factors include venous congestion, which often occurs during radical neck dissection and spine surgery performed in the Trendelenburg position (19). Increased intraocular pressure also may contribute to the development of AION and is

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RAPD, relative afferent pupillary defect.
commonly associated with spine surgery in the prone position (20). Finally, patient-specific vasculopathic risk factors that compromise optic nerve perfusion may be causative and include diabetes mellitus, obesity, and hypertension (16,17,21,22). A small cup-to-disc ratio (disc at risk) may also be a patient-specific risk factor (23,24).

Currently, there are no methods proven effective at preventing perioperative ION. Given that intraoperative hypotension and anemia are reported risk factors, numerous preventative techniques have been suggested to address these issues. Potential strategies include careful monitoring and regulating blood pressure, maintaining hematocrit above 30%, minimizing larger crystalloid infusion, positioning the head above the heart, and dividing prolonged surgeries into shorter staged procedures (13). There is no recommended transfusion threshold to eliminate the risk of vision loss (25). Although monitoring of intraoperative optic nerve function has been proposed as a means of detecting optic nerve ischemia, there is no reliable technique to perform this monitoring because the use of visual evoked potentials has been shown to be unreliable in anesthetized patients (26–28). Current recommendations from the American Society of Anesthesiologists Task Force on Perioperative Blindness incorporate many of the hemodynamic preventive strategies described above and suggest that patients undergoing high-risk procedures be informed of a small chance of vision loss during surgery (25).

Our case highlights the difficulty in predicting who will develop ION and also illustrates the importance of patient-specific risk factors for perioperative ION. Surgeons, anesthesiologists, ophthalmologists, and patients should be cognizant that perioperative ION after one surgery may increase the risk of ION after subsequent surgeries.

REFERENCES
Papilledema as the Initial Presentation of Castleman Disease

Guohong Tian, MD, PhD, Yun Jing, MD, PhD, Hanqiu Jiang, MD, PhD, Jingwen Wang, MD, PhD, Xiaojun Zhang, MD, PhD

Abstract: Castleman disease is a rare lymphoproliferative disorder that has many presentations ranging from unifocal or multifocal mass lesions to a monoclonal gammopathy. It has features that may overlap with osteosclerotic myeloma or POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes) syndrome. We report a patient with papilledema, enlarged lymph nodes, and monoclonal IgG, who subsequently developed a polyneuropathy. Biopsy of enlarged mediastinal lymph nodes confirmed the diagnosis of Castleman disease.

doi: 10.1097/WNO.0000000000000096

Castleman disease, also known as angiofollicular lymph node hyperplasia or giant lymph node hyperplasia, is characterized by overgrowth of lymph node tissue at a single site or throughout the body. It can mimic a number of benign and malignant disorders, including POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes) syndrome, lymphoma and myeloma. The initial presentation of papilledema without evidence of polyneuropathy and skin lesions differentiates our patient from POEMS syndrome, although peripheral nerves were involved at a later stage of the clinical course.

CASE REPORT

A 28-year-old woman complained of bilateral blurred vision for 2 months. She also reported occasional transient visual obscurations while changing positions and frequent pulsatile tinnitus at night. She denied headache, eye pain, fever, skin rash, and joint pain. She was a healthy, slim young woman and had given birth to a boy 3 months previously. She had not been taking oral contraceptives, systemic corticosteroids, or vitamin A derivatives. She reported a recent unintentional weight loss of 5 kg.

Neuro-ophthalmological examination revealed the patient to be alert and oriented. Visual acuity was 20/60, right eye, and 20/20, left eye. Pupils were equal in size with a right relative afferent pupillary defect. Eye movements were full and visual fields showed generalized contraction, more so in the right eye. Ophthalmoscopy revealed diffuse edema of both optic discs with peripapillary hemorrhages, and macular exudates (Fig. 1).

Brain magnetic resonance imaging (MRI) demonstrated an empty sella and dilation of the optic nerve sheaths without enhancement of the optic nerves (Fig. 2). Magnetic resonance venography was normal. The opening pressure on lumbar puncture was 450 mmH₂O. The cerebrospinal fluid (CSF) was acellular with normal glucose (2.79 mmol/L, normal: 2.5–4.4 mmol/L), chloride (126.6 mmol/L, normal: 120–130 mmol/L), and elevated protein (71 mg/dL, normal: 15–56 mg/dL). Other laboratory tests showed: white blood cell (WBC) 5.4·10⁹/L, red blood cell 3.26·10¹²/L, hemoglobin 108 g/L, erythrocyte sedimentation rate (ESR) 35 mm/h, C-reactive protein (CRP) 8.6 mg/L (normal: <5 mg/L), serum free T3 1.71 pmo1/L (normal: 2.0–6.5 pmo1/L), free T4 6.12 pmo1/L (normal: 7.5–15), and thyroid-stimulating hormone 7.5 pmol/L (normal: 0.4–6.5 pmol/L). Serum protein electrophoresis revealed elevated IgG 2,600 mg/dL (normal: 751–1,560 mg/dL), IgA 341 mg/dL (normal: 82–453 mg/dL), and IgM 203 mg/dL (normal: 46–304 mg/dL). IgG monoclonal spike: Kappa 2,520 mg/dL (normal: 629–1,350 mg/dL) and Lambda 150 mg/dL (normal: 313–723 mg/dL). Bone marrow aspirate showed a slight increase in plasma cells, and biopsy of bone marrow was otherwise normal.
Computed tomography (CT) of the chest showed multiple enlarged lymph nodes in the mediastinum and hilum and bilateral hydrothorax (Fig. 3). In addition, the liver and spleen were enlarged on abdominal CT. Lymph node biopsy revealed marked follicular hyperplasia with plasma cell infiltrates consistent with Castleman disease (Fig. 4).

The patient was treated with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) chemotherapy for 4 months without improvement in vision. Repeat lumbar puncture showed an opening pressure of 340 mmH₂O. She started complaining of weakness of her legs, and neurological examination showed sensory deficits in stocking glove distribution and reduced deep tendon reflexes. Electromyography confirmed the diagnosis of motor and sensory peripheral neuropathy. The patient was referred for a clinical trial of rituximab.

FIG. 1. Bilateral papilledema is present with macular exudates.

FIG. 2. Brain magnetic resonance images. Noncontrasted axial T1 (A) and T2 (B) scans show normal brain structures, dilated optic nerve sheathes, and elevated optic discs. Coronal short-tau inversion recovery image (C) shows prominent cerebrospinal fluid signal surrounding the optic nerves while contrast-enhanced axial T1 image (D) reveals no enhancement of the optic nerves.
One year later, visual acuity and fields were stable and optic discs showed pallor and gliosis with blurred margins. The patient became wheelchair bound due to progression of peripheral neuropathy and is being treated with rituximab, acupuncture, and physical therapy.

**DISCUSSION**

In 1956, Castleman et al (1) reported 13 cases of unicentric hyaline vascular disease of the chest with pathologic features of hypervascular lymph nodes containing hyalinized blood vessels. The disease may be unicentric or multicentric depending on the extent of lymph node involvement. Histopathogenetic classification includes hyaline vascular Castleman disease, plasma cell Castleman disease, human herpes virus 8 (HHV-8)–associated Castleman disease, and multicentric Castleman disease, as not otherwise specified (2). Approximately 70% of cases occur in the chest, 15% in the neck, and 15% in the abdomen and pelvis, involving primarily lymphatic tissues.

Our patient’s presenting symptom was blurred vision, associated with transient visual obscurations and pulsatile tinnitus. Her examination was remarkable for bilateral papilledema. The results of her brain MRI and elevated opening pressure on lumbar puncture were consistent with the diagnosis of pseudotumor cerebri. However, the elevated CSF protein and abnormal ESR and CRP led to the diagnosis of papilledema secondary to an underlying systemic disease. The diagnosis of Castleman disease was established from the pathologic features of enlarged mediastinal lymph nodes.

Central nervous system involvement in Castleman disease is uncommon. Since Black et al (3) reported a case of Castleman disease with pseudotumor cerebri in 1988, this association is rare although papilledema and increased intracranial pressure are noticed in many cases of the POEMS syndrome, which...

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**FIG. 3.** Contrast-enhanced axial chest computed tomography. **A.** There is mediastinal and paratracheal adenopathy (**arrow**). **B.** A pericardial effusion (**arrowheads**) and a left-sided pleural effusion (**arrow**) are present.

**FIG. 4.** Lymph node biopsy. **A.** Lymph node follicle contains penetrating, longitudinal vessels (**arrow**) and interfollicular regions with plasma cell infiltration (asterisks) (hematoxylin and eosin, ×100). **B.** Germinal center shows “onion skin” appearance (hematoxylin and eosin, ×400). Immunostaining is negative for CD34 (**C**) and positive for CD20 (**D**) (×100).
Clinical Observation

may be associated with plasma cell–type Castleman disease (4–8).

The pathophysiology of papilledema in Castleman disease is unclear, although there are several potential mechanisms. In our case, optic disc swelling was likely due to increased CSF pressure rather than direct cellular infiltration, since the optic nerves did not enhance on MRI. We postulate that increased vascular permeability in our patient led to bilateral hydrothorax, pericardial effusion, and increased CSF volume resulting in intracranial hypertension and papilledema.

Vascular endothelial growth factor (VEGF), which is expressed by osteoblasts, macrophages, and tumor cells (including plasma cells), is known to target endothelial cells, increasing vascular permeability, and stimulating angiogenesis (9,10). It is well known that elevation of the VEGF level in POEMS syndrome is associated with severe symptoms and can be used to monitor disease activity (11–13). In animal models of POEMS, mice that are transplanted with human glioblastoma exhibit high serum levels of VEGF, prominent edema with increased tissue volume, and pathologic findings in the liver, spleen, and kidney (13). Nishi et al (14) showed that the VEGF levels of the serum and supernatant fluid of cultured lymph nodes of 2 Castleman disease patients were higher than those in normal controls. VEGF was strongly expressed in plasma cells in the interfollicular region of the lymph nodes of their patients. These results suggest that this cytokine may be involved in vascular proliferation in the interfollicular region of the lymph nodes of the plasma cell–type Castleman disease. Increased VEGF may affect the blood–brain barrier by increasing permeability. Other upregulated cytokines, such as matrix metalloproteases, may cause additional exudation of fluid and intracranial hypertension.

Our patient’s initial clinical findings extended beyond multicentric lymph node involvement and included organomegaly, endocrinopathy, and monoclonal gammopathy. She eventually developed motor and sensory polyneuropathy. While not satisfying the diagnostic criteria for POEMS syndrome (15), our case illustrates a wide spectrum of pathologic and clinical manifestation, which might be considered an overlap syndrome (16).

We have no experience with the use of carbonic anhydrase inhibitors as an add-on therapy to reduce the intracranial pressure in Castleman disease. Our patient’s blood while cell count dropped dramatically after a single dose of methazolamide (100 mg) and, therefore, was discontinued.

Long-term studies are needed in patients with Castleman disease to evaluate the efficacy of systemic chemotherapy, as well as targeted anti-monoclonal CD20 antibody and anti-VEGF therapy (17,18).

REFERENCES

Primary Atypical Optic Nerve Sheath Meningioma in a Child With Restricted Diffusion on Magnetic Resonance Imaging

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Abstract: Optic nerve sheath meningioma is most often discovered in adults and is relatively rare in children. We report a 12-year-old girl with an atypical primary optic nerve meningioma, which demonstrated restricted diffusion on magnetic resonance imaging and high Ki67 labeling index. The patient developed recurrence, despite aggressive surgical resection of primary tumor and local radiation. We are unaware of previous reports documenting this constellation of imaging and histopathologic findings.


Optic nerve sheath meningioma is a tumor arising within the nerve sheath of the orbital or intracanalicular portion of the optic nerve secondary to proliferation of meningothelial cells. This tumor may be either a primary tumor of the optic nerve sheath or more commonly secondary tumor because of extension of a primary intracranial meningioma into the orbit (1,2). Its occurrence is relatively rare in the pediatric patients and has more aggressive behavior in this population (1). We report an atypical primary optic nerve meningioma, which demonstrated restricted diffusion on magnetic resonance imaging (MRI) and high Ki-67 labeling index.

CASE REPORT

One year before admission to hospital, a 12-year-old girl noted blurred vision in her left eye, which progressed to complete visual loss with no light perception. She initially was diagnosed with optic neuritis and received a course of corticosteroids without improvement. The patient was later thought to have a “blood clot” behind her eye based on an outside imaging study and was started on enoxaparin. She continued to have pain behind her left eye and a subjective feeling of her eye being “pushed out.” She was referred to our institution, where an MRI revealed a fusiform left orbital intraconal, a mass producing moderate degree of proptosis of the left globe (Fig. 1). The mass had a homogeneously low-signal intensity on T2 images filled most of the intracranial space with evidence of intraocular invasion. Avid enhancement of the mass was demonstrated after contrast administration, which extended through the left optic canal involving the intracranial left optic nerve just anterior to the optic chiasm. The mass also demonstrated restricted diffusion (Fig. 2). The lesion was biopsied, followed by exenteration of the left orbit with reconstruction of the socket with dural fat graft. This tumor had the histologic features and immunohistochemical staining characteristics of a meningioma. The Ki67 labeling index was at least 10% (Fig. 3). The neoplasm also demonstrated an extremely aggressive pattern of growth with invasion of the orbit, retina, and choroid and near total replacement of the optic nerve (Fig. 4). The constellation of histopathological and immunohistochemical findings was consistent with atypical meningioma.

A left orbitozygomatic craniotomy was performed for removal of the remaining tumor in the apex of the orbit, and optic canal, followed by local radiation to the tumor bed (5940 cGy). Five years later, the patient presented with tumor recurrence in the floor of the left orbit with bone destruction and extension into the left maxillary sinus. This was successfully treated with resection and radial-free flap reconstruction. The patient has had multiple neuroimaging studies and shows no signs of...
tumor recurrence 36 months after her last surgery. No evidence of neurofibromatosis type 2 or other meningiomas have been detected in our patient.

**DISCUSSION**

A significant feature of meningiomas in childhood is the higher rates of malignant and atypical subtypes in comparison with adults (3,4). In one report, 25% of all meningiomas in the pediatric population showed biological aggressive behavior in terms of disease progression (4). Our patient fit this clinical profile. The main differential diagnoses in a child presenting with an optic nerve tumor are optic nerve glioma and optic nerve meningioma. In our case, complete involvement of optic nerve and restricted diffusion on MRI was also suggestive of a primitive neuro-ectodermal tumor such as medulloepithelioma (5).

In the pediatric age group, literature regarding the neuro-imaging appearance of primary optic nerve meningioma is scant, and no specific pattern has been recognized (1). However, most nerve sheath meningiomas in adult patients have a tubular configuration, followed by other patterns including globular, fusiform, or focal enlargement of the optic nerve sheath (1). Irregular tumor margins in the orbit are indicative of extradural invasion into surrounding tissues (1). MRI is the study of choice for evaluation of optic nerve tumors and should include fat suppression sequences and intravenous contrast (6). Lope et al (7) described the diffusion characteristics of a series of orbital tumors in pediatric patients. In one case, a meningioma demonstrated restricted diffusion; however, they did not

**FIG. 1.** Magnetic resonance imaging of atypical optic nerve sheath meningioma. T2 Axial (A) and coronal (B) images reveal a relatively hypointense left intraorbital mass surrounding the optic nerve. Postcontrast T1 axial (C) scan shows avid enhancement of the tumor.

**FIG. 2.** Diffusion-weighted images demonstrate restricted diffusion (arrows) in trace diffusion image (A) and ADC map (B).
generate apparent diffusion coefficient (ADC) values and did not determine the histological type and grade or comment about primary optic nerve meningioma vs extension form an intracranial meningioma.

Multiple studies have found a statistical significance between histopathological subtype of meningiomas and the ADC values, with a tendency for atypical/malignant tumors to have lower ADC values (8,9). Various theories have been

FIG. 3. Histopathologic specimen. A. The tumor is composed of meningothelial cells arranged in whorls and small lobules (hematoxylin and eosin, ×200). B. There are scattered mitotic figures (arrow) (hematoxylin and eosin, ×400). C. The tumor cells stain for epithelial membrane antigen (×400). D. There is prominent proliferative activity with MIB 1-Ki67 index of approximately 10% (MIB1-Ki67, ×400).

FIG. 4. Histopathologic specimen. A. The meningioma invades the retina, choroid and almost completely replaces the optic nerve. Only a thin, atrophic central portion of the nerve is recognizable (arrow) (hematoxylin and eosin, ×5). Nests and lobules of tumor cells infiltrate the optic nerve (arrow) (B) (hematoxylin and eosin, ×100), the sclera and choroid (arrow) (C) (hematoxylin and eosin, ×400) and the retina (arrow) (D) (hematoxylin and eosin, ×100).
proposed to explain the decreased ADC in high-grade tumors including increased tumor cellularity, increased nucleus/cytoplasm ratio, small cell size, fibrous, or gliotic tissues within the tumor or a combination of these factors (10). Ki-67 is an immunohistochemical cell proliferation marker that has been used to differentiate between benign and atypical/malignant meningiomas. In addition, this marker has been shown to be a more reliable predictor of both tumor recurrence and patient survival than histologic grade (11,12). A cutoff Ki-67 index of 10% has been proposed for distinguishing potentially recurrent and nonrecurrent meningiomas (12). In our patient, both restricted diffusion and Ki-67 value were indicative of the malignant nature of the tumor, which recurred despite aggressive initial resection and local radiation.

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The Pathophysiology of Thyroid Eye Disease

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Abstract: The pathophysiology of thyroid eye disease (TED) is complex and incompletely understood. Orbital fibroblasts (OFs) seem to be the key effector cells that are responsible for the characteristic soft tissue enlargement seen in TED. They express potentially pathogenic autoantigens, such as thyrotropin receptor and insulin-like growth factor-1 receptor. An intricate interplay between these autoantigens and the autoantibodies found in Graves disease may lead to the activation of OFs, which then leads to increased hyaluronan production, proinflammatory cytokine synthesis, and enhanced differentiation into either myofibroblasts or adipocytes. Some of the OFs in TED patients seem to be derived from infiltrating fibrocytes. These cells originate from the bone marrow and exhibit both fibroblast and myeloid phenotype. In the TED orbit, they may mediate the orbital expansion and inflammatory infiltration. Last, lymphocytes and cytokines are intimately involved in the initiation, amplification, and maintenance of the autoimmune process in TED.

doi: 10.1097/WNO.0000000000000132

Thyroid eye disease (TED) is a vision-threatening condition that is most commonly associated with Graves disease (GD). Although the mechanism underlying the thyroid gland dysfunction in GD is now relatively well-characterized, the pathophysiology of TED is only beginning to be elucidated (Fig. 1). The common finding in TED that accounts for most of its clinical manifestations seems to be enlargement of orbital soft tissues (1). Radiographic evidence suggests an increase in the volume of both muscle and orbital fat (2). Histopathologic studies of the TED orbit reveal an extensive deposition of hyaluronan (a hydrophilic glycosaminoglycan) between muscle fibers, a widespread inflammatory infiltrate, and an overabundance of cytokines (3,4). These changes lead to interstitial edema and soft tissue expansion. Confined within the rigid orbital walls, such tissue enlargement can lead to increased intraorbital pressure, mechanical compression of orbital tissue including the optic nerve, and further inflammation (1).

ROLE OF ORBITAL FIBROBLASTS

The principal cell type responsible for the enlargement of orbital soft tissues in TED seems to be the orbital fibroblast (OF) (5–10). These cells are located in the interstitial space between muscle fibers, and within orbital fat and connective tissues (11). There are 2 subpopulations of OFs, which are classified based on whether or not they express the surface marker Thy1/CD90 (8,9,12,13). Thy1-expressing (Thy1+) OFs reside in the perimysium of the extraocular muscles. When activated, they can differentiate into myofibroblasts, the contractile element found in wound healing (12). Thy1-deficient (Thy1−) OFs are preadipocytes found throughout the orbit and can differentiate into mature adipocytes (8,12,14–17). The relative proportion of activated Thy1+ and Thy1− OFs may determine whether fibrosis or adipogenesis predominates in TED (8,12). In vitro studies have demonstrated that OFs from patients with TED (TED-OFs), more than those from healthy controls, are prone to activation, leading to proliferation, hyaluronan secretion, and soft tissue expansion (18–28). As will be discussed below, some OFs have robust expression of thyrotropin receptor (TSHR) and insulin-like growth factor-1 receptor (IGF-1R), 2 autoantigens that are thought to contribute to the activation of OFs in TED. Finally, TED-OFs are both more capable of secreting and responding to inflammatory cytokines compared with controls, possibly leading to amplification of the disease process (8,21,29–34).

ROLE OF FIBROCYTES

Fibrocytes are bone marrow–derived, fibroblast-like progenitor cells that circulate in the peripheral blood and may play a role in the pathogenesis of TED. They express the...
hematopoietic stem cell marker CD34 and the leukocyte common antigen CD45, and also various fibroblast proteins such as alpha-smooth muscle actin, collagen I and III, fibronectin, and vimentin (35). Fibrocytes are capable of migrating to sites of injury and differentiating into fibroblasts or adipocytes, participating in tissue remodeling and induction of T-cell proliferation (36,37). With both tissue-remodeling properties of fibroblasts, and proinflammatory properties of macrophages, fibrocytes have been implicated in various inflammatory or autoimmune-related fibrotic processes (38).

Fibrocytes are significantly more abundant in the peripheral circulation of patients with GD compared with healthy controls (39). Moreover, they have been shown to infiltrate both the orbital and thyroid tissues in GD patients (39,40). Within the orbit, fibrocytes exhibit remarkable plasticity and, similar to OFs, can differentiate into adipocytes or myofibroblasts (41). Furthermore, fibrocytes can be activated to produce cytokines in a similar manner as OFs. Patients with TED have markedly increased prevalence of CD40+ fibrocytes (42), which, in response to CD40 ligand, can produce interleukin (IL)-6, IL-8, macrophage chemoattractant protein 1, chemokine ligand 5 (CCL5), and tumor necrosis factor alpha (TNF-α), a profile very similar to that of activated OFs (42). Fibrocytes also resemble OFs in that they express both TSHR and IGF-1R on their surface. The potential functional relevance of this finding is discussed below. In

FIG. 1. Pathophysiology of thyroid eye disease (TED). Self-tolerance to thyrotropin receptor (TSHR) and insulin-like growth factor-1 receptor (IGF-1R) is lost for unclear reasons. Antigen-presenting cells internalize TSHR and IGF-1R and present them to helper T cells, which become activated and may either induce B cells to produce autoantibodies isolated from serum of GD patients (GD-IgGs), or become autoreactive T cells. GD-IgGs interact with TSHR on thyroid follicular epithelial cells, leading to follicular hyperplasia and hypertrophy. Autoreactive CD4 T cells can travel to orbital tissues in response to T-cell chemoattractants and interact with orbital fibroblasts (OFs). This interaction leads to the mutual activation of both cell types. Various inflammatory cytokines are secreted by T cells, B cells and OFs. Each of these cell types also overexpress IGF-1R, which can interact with GD-IgGs, resulting in cellular activation. On the surface of OFs, IGF-1R and TSHR form a physical and functional complex that interacts with GD-IgGs. Some of the OFs in TED patients may be from infiltrating fibrocytes derived from the bone marrow. Activated OFs can differentiate into either adipocytes or myofibroblasts, and have increased hyaluronan synthesis. Together, these processes lead to the expansion of orbital soft tissues in TED.
aggregate, the above evidence introduces fibrocytes as a potential player in the pathogenesis of TED. Studies to further delineate the precise role of fibrocytes in TED are ongoing.

**ROLE OF AUTOANTIGENS**

OFs become abnormally activated in TED in both an antigen-dependent and antigen-independent manner. Several potential autoantigens have been identified in TED, although very few show any correlation with the presence or severity of TED (43–49). Nonetheless, 2 proteins that show significant promise as pathogenic autoantigens in TED are TSHR and IGF1-R.

**Role of Thyrotropin Receptor**

Thyrotropin receptor and its autoantibodies have a well-established role in the pathogenesis of GD (50). Accumulating evidence indirectly implicates them in the pathogenesis of TED. Autoantibodies against TSHR can be detected in up to 98% of patients with TED (51). Titers of the 2 subtypes of TSHR antibodies, thyroid stimulating immunoglobulins (TSI), which directly activate TSHR, and TSHR binding inhibitory immunoglobulins (TBI), which prevent TSH from binding TSHR, are both positively correlated with the clinical activity and severity of TED (47,48,51–53). It is unclear how these autoantibodies with seemingly opposite mechanisms of action on TSHR would positively correlate with each other and with the severity of disease. One hypothesis is that they may serve as a nonspecific marker of the B-cell–mediated autoimmune response.

The expression of TSHR, once thought to be limited to thyrocytes, has now been reported in a variety of cell types throughout the body, albeit at very low levels (54). Orbital tissues and primary cultures of OFs from patients with TED have increased TSHR expression compared with those from healthy controls (55–58). Moreover, TSHR expression in TED orbital tissues is higher in active disease compared with inactive disease (59). Although fibrocytes from both TED patients and healthy controls express TSHR, the fraction of TSHR-expressing fibrocytes is also significantly increased in the peripheral circulation of patients with TED (42). These TSHR-expressing fibrocytes from TED patients have an extremely high expression of TSHR per cell, rivaling thyrocytes (39,40,42). The mechanism underlying TSHR overexpression in OFs and fibrocytes remains unclear, but the above correlational evidence suggests the possibility that TSHR and its autoantibodies are involved in the pathogenesis of TED.

In vitro studies with cultured OFs yield further evidence that TSHR is a pathogenic autoantigen in TED. Treating Thy1-OFs (preadipocytes) with TSH or a stimulatory TSHR antibody, M22, leads to enhanced adipocyte differentiation as evidenced by increased expression of late-adipocyte genes adiponectin and leptin (60). On differentiation into mature adipocytes, these cells further increase the expression of TSHR, more so in TED-OFs than controls, which may contribute to the maintenance of disease (8,14–16,55,60–62). This TSHR-antibody–mediated activation of TED-OFs can be attenuated by a small molecule antagonist of the TSHR (63). Conversely, OFs transfected with a constitutively active TSHR mutant construct show stimulated hyaluronan production and early differentiation into adipocytes (64,65). The upregulation of TSHR in fibrocytes also seems to have a functional significance, as treatment of these cells with TSH leads to the production of the proinflammatory cytokines, TNF-α and IL-6 (39,40,42). The collective in vitro evidence above suggests that TSHR is a key pathogenic autoantigen in TED.

Several in vivo models of GD have been developed in recent decades, using various means to immunize mice with TSHR and induce TSHR antibody production (66–70). Although these models were able to produce hyperthyroidism, the orbital soft tissue changes as seen in TED were either not assessed or not present (66–70). An animal model with orbital features analogous to TED was recently reported. This model was generated by immunizing female BALB/c mice by in vivo muscle electroporation with the extracellular ligand-binding domain of TSHR (71,72). All immunized mice produced measurable TSHR antibodies, although most produced TBIIs rather than TSIs, and the mice developed hypothyroidism rather than hyperthyroidism (71). Nevertheless, immunized mice developed orbital changes that clinically, radiographically, and pathologically resembled those observed in humans with TED (71). This study provides the strongest in vivo evidence to date supporting an integral role of TSHR in the pathogenesis of TED.

**Role of IGF-1R**

Another potentially pathogenic autoantigen in TED is the IGF-1R. This receptor tyrosine kinase and its signaling pathway have a wide spectrum of functions in tissue growth and development, and may participate in the pathogenesis of several metabolic, neoplastic, and immunologic diseases (73–77). The expression of IGF-1R is increased in TED-OFs compared with that in controls (78). The fraction of IGF-1R-expressing fibrocytes also seems to be increased in TED (39). When TED-OFs, but not control OFs, are treated with IGF1, they become activated and upregulate hyaluronan synthesis, similar to the response observed in these cells when treated with TSHR antibodies (25,79). This raises the possibility that IGF1 and TSHR antibodies may act through the same pathway. In addition, after the addition of IGF-1 or autoantibodies isolated from serum of GD patients (GD-IgG), TED-OFs, but not the control OFs, produce 2 powerful T-cell chemoattractants, IL-16 and CCL5 (80,81). On the contrary, recombinant human TSH could not induce this particular response in TED-OFs (80). This suggests that the GD-IgGs may be capable of
activating the TED-OFs through a pathway independent of the TSHR, namely, the IGF-1R pathway (80).

There is increasing in vitro evidence now supporting the role of the IGF-1R pathway in the pathophysiology of TED. GD-IgGs can displace IGF1 from its high-affinity binding site on the cell surface of OFs (82). Although this binding site has not been confirmed to be a part of the IGF-1R, its dissociation constant is similar to that previously reported for IGF-1R (82–85). This suggests that GD-IgGs have an IGF-1R binding component. When IGF-1R function is disrupted in TED-OFs, either through the treatment with an IGF-1R blocking antibody or transfection with a dominant negative mutant IGF-1R, the GD-IgG–induced activation of TED-OFs is attenuated (81). Therefore, it seems that the GD-IgGs exert their effects on the TED-OFs at least in part through the IGF-1R pathway. The exact component of GD-IgGs that may be interacting with the IGF-1R is unknown. Autoantibodies against IGF-1R have been identified but have similar prevalence in TED patients and healthy controls, and the antibody concentration does not correlate with TED severity (86). Two mouse models of GD reported that some mice developed low titers of IGF-1R antibodies after immunization with TSHR (71,87). Interestingly, mice immunized with IGF-1R do not develop any obvious pathology, suggesting the importance of the thyroid autoantigens (71). Finally, it is possible that TSHR autoantibodies are the entities in GD-IgGs that are cross-reacting with IGF-1R.

IGF-1R and TSHR may work in a concerted fashion in the pathogenesis of TED. The IGF-1 and TSH have long been known to exert synergistic regulatory influences on target T-cell function, growth, and proliferation (74,88–90). This may in part be explained by the close physical relationship between the 2 receptors (78,91). Immunofluorescence staining shows that IGF-1R and TSHR colocalize to the perinuclear, cytoplasmic, and plasma membrane compartments in thyrocytes and OFs (78). Antibodies against either IGF-1R or TSHR can immunoprecipitate both proteins (78). Furthermore, an IGF-1R–blocking antibody can also block the signaling initiated by TSH, TSHR stimulating antibody, and GD-IgGs in TED-OFs (78,92). Whether or not these findings are due to antibody cross-reactivity between the 2 receptors is unclear. Studies to further characterize the physical and functional relationship between IGF-1R and TSHR and its implications in TED are ongoing.

**ROLE OF LYMPHOCYTES**

It is not known what initiates the immune response against autoantigens in autoimmune diseases. Factors such as susceptible genetic polymorphisms and environmental triggers such as infection have been proposed to contribute to this process in TED, but none have been definitively proven (93). Both T cells and B cells are intimately involved in the autoimmune response. Antigen-presenting cells present a pathogenic epitope of an autoantigen to CD4+ helper T cells, leading to T-cell activation and proliferation. The activated T cells may then either induce and sustain B cells to produce antibodies against the autoantigen, or be involved directly as autoreactive T cells in inflammation and/or cellular destruction (94). The tissue damage in autoimmune diseases arise from either direct attack by autoantibodies or autoreactive T cells, immune complex formation, or from local inflammation (94). Autoantibodies may also bind to receptors on target cells, causing enhanced activation or suppression of their signaling pathways (e.g., TSHR antibodies), leading to cellular dysfunction (94).

All of the aforementioned autoimmune processes likely partake in the pathophysiology of TED. Current evidence sheds light on a few more specific ways in which the T cells and TED-OF interact. Activated TED-OFs can produce potent T-cell chemoattractants, IL-16 and CCL5, facilitating the recruitment of T cells to the orbit (80,81). Once there, the T cells can reciprocate and activate TED-OFs either through cell–cell interaction or through diffusible cytokines. For example, the CD4+ T cells express CD145 (also known as CD40 ligand) on their cell surface. This ligand binds to CD40, a T-cell costimulatory protein expressed on the surface of TED-OFs in a higher amount as compared with controls (33). When treated with the cytokine interferon γ (IFN γ), TED-OFs increase their expression of CD40 even further (33,95). The binding of CD145 to CD40 triggers the activation of both the T cells and the TED-OFs. Activation of the T cells allows for the development of their effector functions including induction of B-cell differentiation and activation of monocytes and macrophages (96). The CD40–CD154–induced activation of TED-OFs lead to cell proliferation (97), increased synthesis of hyaluronan and prostaglandins (21), and production of proinflammatory cytokines including IL-6, IL-8, and macrophage chemoattractant protein-1 (33,95). These T-cell–mediated events contribute to the soft tissue remodeling and local inflammatory response in TED.

The principal functions of B cells include antibody production, antigen presentation, and cytokine production. B-cell-deficient mice fail to generate T-cell-mediated responses after immunization with TSHR (98). Therefore, B cells are indispensable to the initiation of the autoimmune process in GD. Rituximab is a monoclonal antibody that binds to the B-cell surface antigen CD20. The treatment of B cells with rituximab leads to the attenuation of CD20-dependent B-cell maturation, and reduced B-cell–mediated antigen presentation and cytokine production (99). More nonrandomized trials and case series have suggested that rituximab can induce lasting clinical improvement in TED (100–106). This confirms the critical role of B cells in the pathogenesis of TED. Several randomized controlled clinical trials are underway to further assess the efficacy and safety of this novel therapy for TED.
The expression of IGF-1R on T cells and B cells may further contribute to the autoimmune response against OFs in TED. A significantly higher fraction of the T-cells and B cells in GD patients expresses IGF-1R as compared with controls (107,108). This is evident in T cells from the blood and orbit (107), and in B cells from the blood, orbit, and bone marrow in these patients (108). Studies on discordant monozygotic twins show that this increase in the fraction of IGF-1R+ T cells and B cells in GD is not due to genetic determinants (109). For the T cells, display of IGF-1R protects these cells from apoptosis and promotes survival (107). For the B cells, increased IGF-1R display facilitates clonal expansion and propagates antibody production (108). These IGF-1R-mediated effects may contribute to the maintenance of the autoimmune response in TED.

ROLE OF CYTOKINES

Cytokines are small secreted proteins that are responsible for modulating the immune system. They are produced by each of the cell types discussed in this review. The aberrantly abundant expression of cytokines plays a central role in the pathogenesis of TED (110–116). There are 2 groups of cytokines: Th1-type (also known as type-1) cytokines produce proinflammatory responses, whereas Th2-type (also known as type-2) cytokines are essentially anti-inflammatory but can influence the production of antibodies (117). Different cytokine profiles are found in orbital tissues from TED patient with different stages of disease (111,118). In the early active stage of TED, Th1 cytokines such as IL-2, IFN-γ, TNF-α predominate (119). These proinflammatory cytokines can recruit more immune cells and amplify the immune response within the orbit (59,118,120). In the later, more inactive, stage of TED, Th2 cytokines such as IL-4, IL-6, IL-10, IL-13 predominate, and collectively, they stimulate B-cell proliferation and maturation into plasma cells, increasing antibody production (111,118,119). Furthermore, Th2-dominated inflammatory responses have been well-documented to lead to fibrosis in various tissues including the heart, liver, and lungs (121–128). Thus, the overexpression of Th2 cytokines may also contribute to the fibrotic changes seen in the later-stage of TED.

An integral event in the pathogenesis of TED is cytokine-mediated activation of the OFs. Interestingly, OFs in culture exhibit a phenotype distinct from fibroblasts derived from other tissues such as the skin or lung; they show more exaggerated inflammatory response to cytokines (8,10,97,129). The TED-OFs and normal OFs have similarly exuberant response to activation by proinflammatory cytokines. Their activation by IL-1α, TGF-β, and leukoregulin leads to drastically increased synthesis of hyaluronan (19,20,24,27) and prostaglandins (29,30). Other activating effects of the cytokines on normal and TED-OFs have also been demonstrated. TGF-β can stimulate the differentiation of the Thy1+ subgroup OFs into myofibroblasts (12). IL-6 can promote adipogenesis and increase the expression of TSHR on Thy1+ OFs (61). Nevertheless, normal and TED-OFs have been shown to respond differently to a few cytokines. The proliferative capacity of TED-OFs was enhanced significantly more than normals in response to cytokines IL-1, IL-4, IGF-1, TGF-β, and platelet-derived growth factor (28). Furthermore, IL-1 stimulated hyaluronan secretion much more in TED-OFs than in normal OFs (26). Thus, TED-OFs may be even more sensitized to activational cues from cytokines than the already highly responsive normal OFs.

Another unique phenotype of the OFs is that on activation, they are fully capable of cytokine expression. TED-OFs produce higher levels of the proinflammatory cytokine IL-1 and lower levels of the neutralizing interleukin-1-receptor antagonist compared with normal OFs (130). This imbalance may lead to poorly opposed IL-1 signaling and an exaggerated inflammatory response. Other proinflammatory cytokines produced by activated TED-OFs include IL-6, IL-8, and macrophage chemoattractant protein-1 (8,33). Moreover, TED-OFs, but not normal OFs, express high levels of T-cell chemoattractants IL-16 and CCL5 when activated by treatment with IL-1 (34) or GD-IgGs (80), recruiting more inflammatory cells to the local tissue. Last, when treated with leukoregulin, IL-1, or recombinant CD40 ligand, TED-OFs are induced to express extremely high levels of prostaglandin E2, which is a potent mediator of inflammation (21,29–32). Collectively, this evidence solidifies the role of the OFs as the key effector cells in TED with a pronounced ability to respond to activating signals and a propensity to produce more proinflammatory signals of their own, hence generating the vicious cycle where inflammation begets more inflammation.

CONCLUSIONS

TED is an enigmatic vision-threatening autoimmune condition. Although our understanding of its pathophysiology has grown significantly in recent years, much remains to be discovered. Current evidence supports a central role of the OFs in the pathogenesis of TED. They become aberrantly and robustly activated in TED. The mechanism underlying this activation likely involves the autoantigens TSHR and IGF-1R and the GD autoantibodies, as well as interaction with immune cells and proinflammatory cytokines. Fibrocytes are progenitor cells that infiltrate the orbit and differentiate into OFs in TED, contributing to the pathogenesis of TED. As the disease mechanisms of TED continue to become elucidated, therapies that alter the course of disease can be developed.

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Thyroid Eye Disease: Therapy in the Active Phase

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Background: The management of active thyroid eye disease (TED) can be a challenging therapeutic dilemma. The pathogenic complexity, disease heterogeneity, clinical unpredictability, and ocular morbidity associated with TED necessitate a team approach.

Evidence Acquisition: A literature search ending on December 31, 2013, was performed using PubMed (http://www.ncbi.nlm.nih.gov/pubmed) with the following search terms: Graves’ disease, hyperthyroidism, hypothyroidism, Graves’ orbitopathy, Graves’ ophthalmopathy, thyroid eye disease, thyroidectomy, antithyroid medications, radioactive iodine, orbital decompression, orbital radiotherapy (ORT), proptosis, and optic neuropathy. The search included manuscripts in English only. Additional articles and textbooks were retrieved from the reference list of articles that were obtained from the original PubMed literature search.

Results: Corticosteroids, ORT, and orbital decompression have been the mainstay treatment modalities for active TED for more than 50 years. Few randomized controlled studies have systematically evaluated these treatment strategies, and of those trials that have been executed, they are difficult to compare and contrast because of inconsistencies in study design and outcome measures. Newer immunosuppressive and immunomodulating agents are being investigated with anecdotal evidence of improved efficacy compared with traditional treatments.

Conclusions: All patients with TED must be assessed for disease activity and severity to determine the best course of action. Risk factor modification begins with smoking cessation and attaining euthyroid status. The first-line treatment for moderate-to-severe TED or dysthyroid optic neuropathy is systemic corticosteroids; but often a multimodality approach with the addition of ORT or orbital decompression may be required. The development of novel therapeutic agents against specific immunological targets will improve upon the current treatment armamentarium available to clinicians and patients with TED. Uniformly accepted, scientifically reliable and clinically valid outcome measures integrated into well-designed clinical trials are needed to advance the management of TED to a more evidence-based approach.

Graves disease (GD) is the most common autoimmune disorder with the main target of the immune system being the thyroid-stimulating hormone (TSH) receptor of the thyrocyte (1,2). In contrast to most autoimmune diseases that cause targeted tissue damage, the deleterious immunological response in GD results in thyrocyte stimulation and over production of thyroid hormones (3). Thyroid eye disease (TED) is the most common extrathyroidal manifestation of GD (4,5). The extrathyroidal manifestations of GD occur from cross-reaction between activated lymphocytes and cells expressing the TSH and possibly other surface receptors (6). Although the pathogenesis of TED is not clearly understood, most researchers now agree that the orbital fibroblast is the primary point of attack of the immune reaction (7–11). TED may develop before or concomitantly with Graves hyperthyroidism, but in 60% of cases it follows (ranging from months to years) the diagnosis of systemic GD (12,13).

Prevalence and Natural History of Thyroid Eye Disease

The occurrence of clinically evident TED in patients with GD varies greatly from 13% to 69% (14). In a nonintervention, prospective study from a single referral center, over an 8-year period, 346 patients were recruited to determine the prevalence and natural history of TED (15). At presentation, 73.7% of patients had no clinical evidence of TED, 20.2% had mild TED, 5.8% had moderate-to-severe TED,
and 0.3% had dysthyroid optic neuropathy. Of the 194 patients who did not have TED on presentation, after 18 months, 87.1% continued to have no TED, 10.3% developed mild TED, and only 2.6% developed moderate-to-severe TED. Interestingly, of the 43 patients with mild TED on presentation, 58.1% improved spontaneously and only 2.4% progressed to moderate-to-severe TED.

Patients with TED present in 2 distinct phases conceptualized by Rundle curve (Fig. 1) (16,17). The active inflammatory phase is characterized by periorbital edema, conjunctival chemosis, orbital congestion, associated with eyelid retraction, proptosis, and diplopia. The active inflammatory phase is frequently mild and self-limited and often requires only supportive intervention (e.g., artificial tears, sunglasses) (18). The inflammatory phase is typically followed after a variable period (between 6 and 24 months) by a quiet, minimally inflammatory chronic fibrotic phase associated with orbital fibrosis, glycosaminoglycan deposition, and enlarged extraocular muscles. The chronic fibrotic phase results in similar clinical findings (i.e., eyelid retraction, proptosis, and diplopia) to the active inflammatory phase (17).

Treatment of TED has relied on a shotgun approach of general immunosuppression with corticosteroids and orbital radiotherapy (ORT) during the active phase and surgical correction of the anatomic sequelae during the chronic phase. As with other autoimmune diseases, a more contemporary approach to TED focuses on targeted therapies directed at blocking the production or interfering with the activity of specific pro-inflammatory cytokines, manipulating the development, proliferation, and function of specific subtypes of B and T cells and inhibiting adipogenesis (19–21). In TED, such therapies will only be effective in the active inflammatory phase of the disease. Because of the broad clinical overlap of the active and fibrotic phases, it is important to identify, through improved classification schemes, where a patient is situated in the evolution of their disease.

CLASSIFICATION SCHEME AND CLINICAL ASSESSMENT OF THYROID EYE DISEASE

There has been great deal of discussion regarding the classification and assessment of TED for both clinical and research purposes (17,22–26). Given the emerging emphasis on a focused immunosuppression and immunomodulation approach to autoimmune diseases in general, and TED in particular, any such classification or assessment scheme must not only be reproducible but it must be able to accurately score the severity and activity of the inflammatory phase of the disease (27). In 1969, Werner devised the clever mnemonic NO SPECS (No signs and symptoms, Only signs, Soft tissue involvement, Proptosis, Extraocular muscle involvement, Corneal involvement, and Sight loss), which was the basis of the ophthalmology index for many decades (28–31). Although this classification has been used to document disease severity (its original intention was to summarize the overall [active and chronic] clinical manifestations of TED), it does not adequately identify patients in the active phase of disease (22). Since the development of NO SPECS, a number of other classification and assessment schemes have been developed including VISA (Vision, Inflammation, Strabismus, and Appearance) (32), CAS (Clinical Activity Score) (24,33), and the EUGOGO (European Group On Graves’ Orbitopathy) system (34) (See Supplemental Digital Content, Table E1, http://links.lww.com/WNO/A100). These scoring systems assess inflammatory signs in an attempt to identify patients in the active phase who are most likely to respond to treatment.

TREATMENT OF ACTIVE THYROID EYE DISEASE

There is no consensus as to the best treatment strategy for TED. Management of active TED requires a comprehensive and multimodality approach in which the ophthalmologist and endocrinologist work as a team to develop a specific plan of care (34,35). As mentioned above, the decision to initiate treatment requires a careful analysis of the patient’s ophthalmic status (severity) and determination of whether the patient is in the active or chronic phase of the disease (Fig. 1B). Specific questions to be addressed include:

1. How active and severe is the TED?
2. What TED risk factors can be modified or treated?
3. What is the best management strategy for the Graves hyperthyroidism?
4. What is the optimum treatment for the TED?

Modifiable Risk Factors for Development or Progression of Thyroid Eye Disease

There are many risk factors that can affect the development or progression of TED (Fig. 2) (36). Some of these, such as age, gender, ethnicity, genetics, and thyrotropin receptor antibody status, are not modifiable (37,38). Others, such as smoking and thyroid status, can be modified with a potential favorable impact on the course of the disease (4,38).

Smoking

There is strong clinical evidence that cigarette smoking is associated with and adversely affects the development, progression, and management of TED (39). In a case–control study of 450 thyroid patients (with 400 controls), smoking cigarettes increased the risk of TED by 7-fold (40). Smoking has been associated with more severe and progressive TED (34), worsening of TED after radioactive iodine (RAI) treatment (41), and lessening the beneficial effects of immunosuppressive therapy (38,42).

Thyroid Status

As with the cessation of smoking, it is important to achieve and sustain a euthyroid state in patients with TED (38).
Prummel et al (43) found that patients with hyperthyroidism or hypothyroidism had a greater eye severity score than euthyroid patients, which translated to an odds ratio of 2.8. It has also been shown that restoring euthyroidism can improve TED (44).

**Treatment of Hyperthyroidism**

There are 3 main treatment options for patients with Graves hyperthyroidism: antithyroid drugs, thyroidectomy, and RAI treatment (45). Each of these modalities has been studied in terms of the influence on the development and worsening of TED.

**Antithyroid Drugs**

The thionamides (propylthiouracil, methimazole, and carbimazole) lower thyroid hormone production by inhibiting the iodination of thyroglobulin and ultimately the production of thyroxine (T4) and triiodothyronine (T3) (46). Several studies have shown that antithyroid drugs do not adversely affect TED (34,47,48). Bartalena et al (49) studied the effect of methimazole on the development and progression of TED. Of the 148 patients treated with methimazole, 95% had no change in TED status, 3% improved, and only 3% worsened.

**Thyroidectomy**

The effect of thyroidectomy on the course of TED remains unclear (34). Marcocci et al (50) performed a case–control study in which 30 patients with either no or mild TED treated with near total thyroidectomy were compared with 60 patients treated with methimazole. One patient (3.3%) in the thyroidectomy group had new or worsening TED compared with 2 patients (3.3%) in the methimazole group. The authors concluded that near-total thyroidectomy did not have an effect on TED. In a meta-analysis of 3 randomized clinical trials involving total thyroidectomy vs subtotal thyroidectomy (51), no difference was found between these 2 surgical procedures on the development or worsening of TED (52–54).

**Radioactive Iodine Treatment**

In 1967, Kriss et al (55) were the first to report the effect of RAI treatment on TED. Since then many retrospective reports have shown a negative effect of RAI treatment on TED (56,57). Approximately 15% of patients may experience new onset or worsening of TED after RAI treatment (See Supplemental Digital Content, Table E2, http://...).
Prophylactic treatment with oral prednisone during and for several weeks following RAI treatment may significantly reduce the risk of the development or progression of TED (49,59,63,64). Although the exact pathomechanism of TED development or worsening after RAI treatment is not precisely known, it has been suggested that there is a change in thyroid autoimmunity with the production of TSH receptor antibodies due to the release of thyroid antigens as the result of RAI-induced tissue damage (17,56).

Supportive Treatment
All patients with TED should be counseled on risk modification, particularly smoking cessation. Although corticosteroids and ORT reduce the active inflammatory symptoms, there is no proven role for these modalities in reducing the risk of disease progression in patients with mild TED (65). Preservative free artificial tears and moisture chambers are very helpful for dry eyes and corneal exposure. Sunglasses can improve photosensitivity. Fresnel prisms (or monocular occlusion) can resolve double vision. Eyelid retraction can be temporarily treated with the injection of botulinum toxin into the levator superioris and Müller muscle complex (66–68).

Medical Treatment
The most common current treatment strategies for active moderate-to-severe TED involve corticosteroids and ORT.

Corticosteroids
Corticosteroids are the most often used therapy for TED. However, the precise dosage, duration, preparation, and route (intravenous [IV], oral [PO], or periocular) of administration remain a matter of opinion and debate (17,69,70). In most cases, corticosteroid use is reserved for patients with active moderate-to-severe TED and dysthyroid optic neuropathy (16,66,71). The response rate with PO corticosteroids is less than IV corticosteroids (60% vs 80%, respectively) (17,72,73). Pooled data have shown that patients who received IV corticosteroids fared better in terms of double vision, ocular motility, and proptosis, with fewer side effects (72). To
date, there have been only 4 randomized clinical trials that have compared the efficacy of PO corticosteroids with IV corticosteroids (See Supplemental Digital Content, Table E3, http://links.lww.com/WNO/A102) (74–78).

Based on a review of the literature, Zang et al (78) recommend a 12-week course of IV methylprednisolone (0.5 g as a single dose per week for 6 consecutive weeks followed by 0.25 g as single dose per week for 6 consecutive weeks, not to exceed a total of 8 g) for patients with active moderate-to-severe TED. EUGOGO performed a multi-center, randomized, double-blinded trial to assess the efficacy and safety of 3 different cumulative doses (2.25, 4.98, and 7.47 g) of IV methylprednisolone over a 12-week period in patients with active moderate-to-severe TED. The 7.47 g group had the greatest positive short-term response in terms of CAS. This benefit did not persist at 24 weeks and was associated with a slightly higher rate of adverse events compared with the lower doses (79). Oral and IV corticosteroid treatment can be associated with significant hepatic, metabolic, cardiovascular, and cerebrovascular side effects and in some cases death. Patients must be monitored carefully with the benefits weighed against the risks (80).

Intravenous corticosteroids can be highly effective in reversing the visual loss due to dysthyroid optic neuropathy and should be instituted before considering alternative therapy, such as orbital decompression (16,66,81,82). The use of corticosteroids concurrently with ORT has been found to be more efficacious than ORT alone (see below) (17,72,73). Some patients can have worsening orbital inflammation during or after ORT, which can be suppressed with a short course of corticosteroids (83).

Selenium
Selenium, through its effects from selenoproteins, plays an important role in cell development and proliferation, oxidative stress protection, and production of T3. Since selenium acts as a potent antioxidant, and oxygen free radicals contribute to the orbital inflammatory process, theoretically it could be of some therapeutic benefit in TED (84,85). In a randomized, double-blinded, placebo controlled trial of mild TED, the overall ophthalmic outcome was better in the selenium (100 μg twice daily) group compared with the placebo group ($P = 0.01$) (86). TED improved in 61% of the selenium group and 36% of the placebo group. TED worsened in 7% of the selenium group and 26% of the placebo group (selenium compared with placebo, $P = 0.01$). Although there were no adverse drug reactions in any patients taking selenium, concerns of selenium toxicity include the increased risk of diabetes mellitus, glaucoma, and neurotoxicity (87–89).

Orbital Radiotherapy
ORT can be effective in TED with an overall response rate of 60% (34,90). However, there remains much debate over the role of ORT in TED (91). The impediment to a general consensus of ORT in TED derives from the paucity of randomized clinical trials, nonstandardized clinical measures and outcomes, conflicting study results, and heterogeneity of study design and patient populations (See Supplemental Digital Content, Table E4, http://links.lww.com/WNO/A103). In general, ORT has been shown to improve ocular motility and possibly periorcular soft tissue changes but not the degree of proptosis (92,93). ORT has not been shown to decrease the risk of disease worsening in patients with mild TED (94,95).

Three randomized controlled trials compared ORT with sham (94,96,97). Gorman et al (97) found no difference in the treatment effect between ORT and sham, but Mourits et al (96) found that ORT was superior to sham. Prummel et al (94) reported that ORT was efficacious in patients with mild TED but did not slow the progression of mild TED to more severe disease.

Five randomized controlled trials compared ORT with corticosteroids in various combinations (98–102). Bartalena et al (98) found that patients randomized to PO corticosteroids and ORT did better than patients randomized to PO corticosteroids alone. Marcocci et al (99) found that PO corticosteroids in combination with ORT was more efficacious than ORT alone. Prummel et al (100) compared ORT with PO corticosteroids and found no difference. Marcocci et al (101) found the addition of IV corticosteroids with ORT was better than PO corticosteroids with ORT. Finally, Ng et al (102) found that ORT in combination with IV corticosteroids was superior to IV corticosteroids alone. The effect of ORT on visual loss due to dysthyroid optic neuropathy has not been studied in a randomized controlled fashion (93). However, there are many reports that have shown dysthyroid optic neuropathy is responsive to either ORT alone or ORT in combination with corticosteroids (34,101,103,104).

The typical ORT protocol for TED is a total of 20 Gy (or 2,000 rads) per orbit fractionated in 10 days (2 Gy/d) over a 2-week period. However, the optimum fractionation, duration, and dosing of ORT remains unsettled, and lower doses seem to perform just as well as higher doses (105). Gerling et al (106) compared 2.4 Gy with 16 Gy of total ORT given over a 16-day period and found no statistical difference between the 2 groups based on 5 predefined outcome measures. In a pilot study, the clinical and radiological effects of low dose (1 Gy/wk) ORT for 10 weeks was explored (107). All 18 patients had improvement in most of the signs or symptoms of TED.

ORT is a relatively safe procedure but should not be recommended in patients with severe uncontrolled hypertension and diabetes mellitus (especially if there is pre-existing diabetic retinopathy) (92). The risk of radiation retinopathy has been estimated to be 1%–2% within the first decade of treatment (93). Cataract formation is also a potential complication of ORT, but in one long-term
study, the risk of cataract development was not associated with ORT (108).

**Surgical Treatment for Thyroid Eye Disease**

In most cases, surgery (orbital decompression, eyelid recession, and strabismus surgery) is indicated for the rehabilitation of patients with stable, nonactive (fibrotic) TED. In active TED, orbital decompression is reserved for patients with severe orbital inflammation, severe proptosis resulting in corneal exposure, uncontrolled glaucoma from orbital congestion, and dysthyroid optic neuropathy (17). Some of the options that need to be considered when performing orbital decompression include (83,109–113):

- Number of orbital walls to be operated upon: 1, 2, or 3.
- Approach: coronal, external, endoscopic, or combined.
- Incision site: extended eyelid crease, transcaruncular, transconjunctival, etc.
- Type of decompression: boney decompression vs fat-only decompression.
- Orbital rim removal with refixation or preservation.

There are multiple retrospective studies that have documented the efficacy of orbital decompression in stabilizing or improving vision in patients with dysthyroid optic neuropathy (103,114–119). Soares-Welch et al (120) reviewed the results of 215 patients (344 eyes) with dysthyroid optic neuropathy that underwent transantral orbital decompression. Of the 205 eyes that had 20/40 or worse vision, 110 eyes (54%) improved by ≥3 Snellen lines and only 8 eyes (2%) lost ≥3 Snellen lines or more.

The timing of when to intervene with orbital decompression, before or after corticosteroid treatment, in patients with dysthyroid optic neuropathy remains unresolved. In the only randomized controlled study that compared IV methylprednisolone (1 g/d for 3 consecutive days, repeated after 1 week followed by a 4-month PO prednisone taper)...

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**FIG. 3.** Treatment algorithm for active thyroid eye disease.
with orbital decompression (3-wall coronal approach) in patients with dysthyroid optic neuropathy. 5 of 9 patients in the IV methylprednisolone group had improvement in vision compared with only 1 of 6 patients in the orbital decompression group. Interestingly, when the nonresponders in each group (88% of the orbital decompression group and 56% of the IV methylprednisolone group) switched therapy (in addition to receiving ORT in some cases), there was an improvement in vision in all but 2 patients. The authors concluded that IV methylprednisolone should be the first-line treatment for patients with dysthyroid optic neuropathy, and if that fails to improve vision, orbital decompression should be offered (81).

**FUTURE TREATMENT OF THYROID EYE DISEASE**

A variety of procedures, anti-inflammatory, immunosuppressive, and immunomodulating agents have been investigated in the treatment of TED, but few have been scrutinized in randomized controlled studies (See Supplemental Digital Content, Table E5, http://links.lww.com/WNO/A104) (86,121–176).

Despite our expanding knowledge of the underlying molecular and immunological mechanism of TED, the unpredictable behavior of the disease and confounding results of clinical studies complicate treatment paradigms. In addition, many published studies have provided a vast amount of data that are difficult to synthesize into specific universally accepted treatment recommendations. Organizations such as EUGOGO (http://www.eugogo.eu), International Thyroid Eye Disease Society (http://thyroideyedisease.org), and Neuro-Ophthalmology Research and Development Consortium (http://www.nordicclinicaltrials.com/nordic) are working diligently on both a national and an international level to develop a unifying clinically applicable system to reliably identify disease phase and accurately measure therapeutic outcomes (177). The efforts of these organizations will hopefully culminate in many global, multi-center, randomized controlled trials that will produce evidence-based data that can be uniformly integrated and analyzed to provide the necessary answers to many of the questions that still remain about the optimum management of TED. Until evidence-based guidelines are developed, we offer a treatment algorithm for patients with active TED (Fig. 3).

**REFERENCES**


Assessment of Optic Nerve Head Drusen Using Enhanced Depth Imaging and Swept Source Optical Coherence Tomography

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Background: Optic nerve head drusen (ONHD) are calcific deposits buried or at the surface of the optic disc. Although ONHD may be associated with progressive visual field defects, the mechanism of drusen-related field loss is poorly understood. Methods for detecting and imaging disc drusen include B-scan ultrasonography, fundus autofluorescence, and optical coherence tomography (OCT). These modalities are useful for drusen detection but are limited by low resolution or poor penetration of deep structures. This review was designed to assess the potential role of new OCT technologies in imaging ONHD.

Evidence Acquisition: Critical appraisal of published literature and comparison of new imaging devices to established technology.

Results: The new imaging modalities of enhanced depth imaging optical coherence tomography (EDI-OCT) and swept source optical coherence tomography (SS-OCT) are able to provide unprecedented in vivo detail of ONHD. Using these devices it is now possible to quantify optic disc drusen dimensions and assess integrity of neighboring retinal structures, including the retinal nerve fiber layer.

Conclusions: EDI-OCT and SS-OCT have the potential to allow better detection of longitudinal changes in drusen and neural retina and improve our understanding of drusen-related visual field loss.


Optic nerve head drusen (ONHD) are acellular deposits of calcium, amino and nucleic acids, and mucopolysaccharides, buried or at the surface of the optic disc (1–3). When located near the surface, drusen can be directly visualized by ophthalmoscopy. Superficial drusen typically confer an irregular lumpy appearance to the optic disc (4). It is hypothesized that some superficial drusen become visible with age as a result of drusen growth or loss of the neural tissue that obscures the drusen. In contrast, when disc drusen are located closer to the lamina cribrosa, they can be difficult to detect and may require imaging for confirmatory diagnosis (5,6). Although ONHD are normally asymptomatic, they are associated with visual field defects in 24%–87% of affected adults (4,5,7). Wilkens et al (8) found that superficial drusen were more commonly associated with visual field defects than deep drusen. The mechanism of drusen-related visual field loss is poorly understood. ONHD typically enlarge slowly throughout life and a slow progression of visual field loss is common (4,5,7). In rare cases, acute decreases in vision can occur due to vascular occlusion (9).

Recent advances in ocular imaging have improved our ability to image ONHD and have provided a means to obtain objective, quantitative measurements of ONHD and neighboring structures, including the retinal nerve fiber layer (RNFL) (5,10). Better in vivo imaging has the potential to improve our understanding of the pathogenesis of drusen-related visual field damage. The purpose of this review was to describe the use of 2 new optical coherence tomography (OCT) methods, enhanced depth imaging optical coherence tomography (EDI-OCT) and swept...
source optical coherence tomography (SS-OCT), and to evaluate their application in the assessment of ONHD.

CURRENT UNDERSTANDING

Prevalence of ONHD
Clinically recognized ONHD are estimated to occur in 0.3% of the population, with both genders affected equally. However, an autopsy series found a higher prevalence of 2.4% (11,12). The discrepancy between the clinical and autopsy findings is likely due to a high prevalence of undiagnosed drusen (4,5). ONHD are usually asymptomatic and therefore tend to present incidentally, either following routine ophthalmoscopy or following detection of an abnormality on visual field testing (13,14). In approximately 75% of individuals, drusen are bilateral, with a higher preponderance in the nasal rather than temporal optic disc sectors (4,15). ONHD appear to vary in prevalence among those of different racial backgrounds, with ONHD less common in those of African and Asian descent compared to other ethnic backgrounds (16,17). ONHD are more common in conjunction with systemic and ocular diseases, such as retinitis pigmentosa, pseudoxanthoma elasticum, and Alagille syndrome (5); yet the majority of patients have no predisposing ocular or systemic conditions (13,14).

Diagnosis
When superficial ONHD are present, they are often detected on ophthalmoscopy. If drusen are located deep in the optic nerve head (ONH), they may not be directly visible or may be confused with disc swelling due to papilledema, ischemic optic neuropathy, or other neurological conditions. Care must be taken to avoid overlooking genuine neurologic conditions, but in most cases, careful examination and supplementary imaging can readily differentiate these disorders and avoid unnecessary neurological investigations (4). The use of imaging devices to differentiate ONHD and papilledema is specifically discussed later in this review.

Etiology
Even though the first histopathological account of ONHD was more than 150 years ago, the mechanism underlying drusen formation is yet to be fully elucidated (4,18,19). It has been proposed that disc drusen might arise as a consequence of abnormal axonal metabolism leading to the deposition of calcium crystals in mitochondria, disruption of axons, and extrusion of mitochondria into the extracellular space with further accumulation of calcified cellular contents (20). There is some support for this concept from histological findings. For example, following surgical excision of a druse, Kapur et al (21) found it to be composed of calcium phosphate [Ca$_3$(PO$_4$)$_2$], which has been observed to be a trigger for cell death.

Congenital anomalies of the ONH have been suggested as possible contributory factors. It has been proposed that the presence of a small scleral canal could lead to interruption of axoplasmic transport and ischemic changes (22), with resultant phosphate-dependent calcification of intracellular neural mitochondria and accompanying extracellular calcium accumulation (21). Nerve fiber degeneration and accumulation of calcified intracellular contents may also occur due to reduced axoplasmic flow secondary to a congenital anomaly of the ONH (23). An increased prevalence of ONHD has been observed in those with a family history, suggesting that ONHD, or an anatomical predisposition to drusen, might be inherited (22).

ONHD-Induced Visual Field Defects
Although disc drusen are usually asymptomatic, they frequently are associated with visual field defects (4,5,7). It is hypothesized that drusen-related visual field loss may occur as a result of mechanical stress on delicate structures within the prelamellar scleral canal (3). In addition, drusen may compress neighboring retinal ganglion cell axons, resulting in retrograde axonal degradation and further ganglion cell death (7). The visual field defects seen in ONHD range from an enlarged blind spot to defects similar to that seen with glaucomatous optic neuropathy (24,25).

Vascular Complications in ONHD
Congestion of the optic disc secondary to ONHD may lead to impaired blood flow and predispose to acute vascular events, such as retinal vein occlusion, retinal artery occlusion, and anterior ischemic optic neuropathy (3). In rare cases, dramatic visual field loss can occur due to vascular complications. In addition, chronic ischemia in parapapillary tissues can result in subretinal neovascularization, even in younger patients (3). Severe visual field loss has also been reported in eyes without evidence of an acute vascular event (4).

ONHD Progression
The size and relative location of ONHD may change over time, as evident from the change from deep buried drusen typical of childhood to the more visible superficial drusen of older age. Visual field defects may also progress, with an age-related increase in both frequency and severity of drusen-related field loss (26,27). Lee and Zimmerman (9) reported a 1.6% per year increase in severity of drusen-related field loss during a 36-month period. Both the location and size of drusen within the optic disc may impact the risk of visual field defect (2,4). It is notable that the relationship between disc drusen and defects of the RNFL and visual field has not been well documented, perhaps due to the limitations of previous imaging technology.
ESTABLISHED IMAGING TECHNIQUES

In addition to ophthalmoscopy, established imaging tests that have been useful for the detection of ONHD include B-scan ultrasonography, fundus autofluorescence (FAF), and spectral domain optical coherence tomography (SD-OCT). Fundus fluorescein angiography has also been used with drusen demonstrating irregular hyperfluorescence during the late frames. B-scan ultrasonography and FAF rely respectively on the hyperechoic and autofluorescent properties of the calcific drusen. We briefly discuss each of these technologies.

B-Scan Ultrasonography

Using B-scan ultrasonography, disc drusen appear as highly reflective round structures that can also be identified by their acoustic shadowing (Figs. 1, 2). B-scan imaging also may reveal additional calcium deposits invisible on ophthalmoscopy (28) and has been found to have good ability to differentiate ONHD and optic disc adema, with superior accuracy compared to modalities, such as FAF and computed tomography (CT) (29). B-scan is fast, relatively inexpensive, and practical enough for use even in children who are unable to sit still for long periods. Ultrasonography also provides some detail regarding the posterior limit of drusen and drusen dimensions; however, it has a relatively poor resolution and provides little information regarding the structural integrity of the neural retina.

Fundus Autofluorescence

FAF makes use of the inherent autofluorescent properties of ONHD. Autofluorescence occurs in macular degeneration due to the natural fluorophores, particularly lipofuscin, within the retinal pigment epithelium. The specific autofluorescent component(s) of disc drusen are not known (12). FAF can be performed using a standard fundus camera with appropriate filters or using a confocal scanning laser ophthalmoscope (cSLO) (Figs. 1, 2). FAF is useful for differentiating ONHD from optic disc adema (30). However, a major disadvantage of FAF is that it performs poorly in detection of deeper, buried drusen (4,31–33).

Fluorescein Angiography

Fluorescein angiography (FA) uses a fluorescent dye and camera to capture information regarding retinal and
choroidal circulation. Pineles and Arnold (34) reported that FA can be used to reliably differentiate between ONHD and optic disc edema, even in cases where drusen were buried. A key characteristic of optic disc edema was the presence of diffuse, early fluorescein leakage. Buried optic disc drusen were evident by late peripapillary staining, which could be circumferential (80%) or nodular (20%). In addition, FA was useful in diagnosing coexisting disc

**TABLE 1.** Comparison of strengths and weaknesses of imaging modalities for the detection of optic nerve head drusen

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Strengths</th>
<th>Weaknesses</th>
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<tbody>
<tr>
<td>B-scan ultrasonography</td>
<td>Able to image deep drusen</td>
<td>Poor resolution</td>
</tr>
<tr>
<td></td>
<td>Noninvasive</td>
<td>No information regarding retinal nerve fiber integrity</td>
</tr>
<tr>
<td>Fundus autofluorescence</td>
<td>Requires only a standard fundus camera with filters</td>
<td>Limited ability to detect deeper buried drusen</td>
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<tr>
<td></td>
<td>Noninvasive</td>
<td>No 3-dimensional images</td>
</tr>
<tr>
<td>Fluorescein angiography</td>
<td>Able to differentiate between ONHD and optic disc edema</td>
<td>Invasive</td>
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<tr>
<td></td>
<td></td>
<td>Small risk of serious allergic reaction</td>
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<tr>
<td>SD-OCT</td>
<td>Relatively easy to operate</td>
<td>Resolution decreases as depth increases</td>
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<tr>
<td></td>
<td>High resolution</td>
<td>Unable to visualize posterior limits of drusen</td>
</tr>
<tr>
<td></td>
<td>Able to differentiate between ONHD and optic disc edema</td>
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<tr>
<td></td>
<td>Quantitative assessment of retinal nerve fiber layer</td>
<td></td>
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<tr>
<td>EDI-OCT and SS-OCT</td>
<td>Able to image the posterior limits and shape of optic disc drusen</td>
<td>SS-OCT is not yet widely available, whereas EDI-OCT can be performed using modified SD-OCT</td>
</tr>
<tr>
<td></td>
<td>Relatively easy to operate</td>
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<td>Quantitative assessment of retinal nerve fiber layer</td>
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EDI-OCT, enhanced depth imaging optical coherence tomography; ONHD, optic nerve head drusen; SD-OCT, spectral domain optical coherence tomography; SS-OCT, swept source optical coherence tomography.
edema and ONHD. But FA is an invasive procedure, and therefore, in cases of diagnostic uncertainty, effective non-invasive alternatives would be preferable.

**Optical Coherence Tomography**

SD-OCT may be used to image ONHD (35), providing high-resolution images compared to techniques such as B-scan ultrasonography and allows measurement of retinal layers, including the RNFL (4,36,37). SD-OCT may be useful for distinguishing between buried ONHD and optic disc edema (29,38). Using SD-OCT, both ONHD and disc edema typically result in elevation of the ONH; the internal optic nerve contour is smooth in cases of disc edema but irregular in cases of ONHD (29). In a study of 92 patients, SD-OCT was able distinguish 45 patients with ONHD from 15 with disc edema and 35 controls (8). It was also noted in this study that RNFL thinning in patients with ONHD was particularly prevalent in the inferonasal and nasal areas (8). Savini et al (39) suggested that a structure known as the subretinal hyporeflective space (SHYPS), which is located between the retinal pigment epithelium and the choriocapillaris may be useful for differentiating ONHD and disc edema. Using OCT, it has been reported that SHYPS thickness is greater in eyes with disc edema compared to those with ONHD (36). SHYPS thickness greater than 464 μm had 85% sensitivity and 60% specificity in distinguishing between the 2 pathologies (36).

Although SD-OCT has shown promise as a tool for detection and diagnosis of ONHD, a disadvantage of conventional OCT technology is that as depth increases, the resolution of SD-OCT decreases, meaning deeper disc drusen are often poorly demarcated (10,35) (Table 1). Imaging the posterior limits of drusen is also difficult due to the hyperreflective anterior surface causing shadowing (5).

**NEW IMAGING TECHNIQUES**

**Enhanced Depth OCT**

EDI-OCT was first reported in 2008 by Spaide et al (40) to address the limitations of conventional SD-OCT for imaging deep ocular structures. The method initially described involved placing the OCT apparatus close enough to the eye to create an inverted view of the fundus (40,41). This places the coherence gate at a deeper plane than its usual position in the vitreous and moves the position of peak sensitivity from near the posterior vitreous in conventional OCT to the inner sclera for EDI-OCT (41). In EDI-OCT, the deeper layers are closer to the zero delay, with the result that these structures have a smaller frequency and lower shift. Using EDI-OCT it is possible to visualize structures 500–800 μm deeper than with conventional OCT.

EDI-OCT has been used to examine the choroid (40), but recently, its application for imaging ONHD has been explored (5,10). Sato et al (5) demonstrated that EDI-OCT had a high ability to detect ONHD, obtaining images of the posterior limits of disc drusen and measuring drusen area. Figure 3 shows an EDI-OCT image of a large optic disc druse. The circumference of the druse is clearly visible, which allows the cross-sectional area of the druse to be calculated. Druse volume could also be calculated from the complete volume scan.

EDI-OCT provides more information regarding the extent of disc drusen than FFA or B-scan ultrasonography. In a prospective comparative cross-sectional study, Merchant et al (10) found that EDI-OCT was able to detect ONHD more frequently than B-scan ultrasonography. When disc drusen were visible on dilated optic disc photographs or stereophotographs, both EDI-OCT and B-scan ultrasonography identified the ONHD. However, in 25 eyes with suspected ONHD, EDI-OCT detected drusen in 17 eyes compared to B-scan which detected drusen in only 7 eyes. Drusen were evident either as signal poor regions surrounded by short hyperreflective bands or as isolated or clustered hyperreflective bands without a signal poor core.

A further advantage of EDI-OCT is that it provides greater ability to assess the shape and structure of the drusen, which may have implications for visual function. EDI-OCT has proved useful for investigating the relationship between drusen and RNFL. Using EDI-OCT, Sato et al (5) found significant negative correlation between the diameter of disc drusen and the global RNFL thickness ($r = -0.61, \ P = 0.001$). In addition, there was a significant positive correlation...
between the disc drusen diameter and the number of sectors of thinned RNFL. Increased presence of drusen within the optic canal was also associated with thinner RNFL (5). It has been proposed that EDI-OCT might also be able to detect early drusen formation, which may be indicated by the presence of deep hyperreflective bands within the ONH (10).

EDI-OCT may also be used in conjunction with cSLO FAF to allow precise localization of the EDI-OCT scan to the region of interest (Figs. 1, 3).

**Swept Source OCT**

SS-OCT such as the deep range imaging OCT (Topcon, Tokyo, Japan) has been introduced recently with several modifications compared to conventional SD-OCT. SS-OCT uses a laser that sweeps across a range of wavelengths to produce an image in almost real-time with a scanning speed of 100,000 Hz at the 1 μm wavelength region (41,42). Despite differences in light source and detection methods, SS-OCT acquisition times are fast since the detector is much simpler (41). Deeper penetration of ocular tissue is achieved by using light of a longer wavelength, which is less affected by light scattering by the photoreceptors and retinal pigment epithelium. The SS-OCT light source has a center wavelength of 1,050 nm, yielding approximately 8 μm axial resolution (42). SS-OCT has been shown to significantly improve visualization of the posterior ocular structures compared to SD-OCT. (C).

**FIG. 4.** Swept source optical coherence tomography of the left eye of a subject with optic nerve head drusen (A, B). The yellow lines on the red-free images indicate the direction of the enhanced depth imaging optical coherence tomography. The corresponding retinal nerve fiber layer thickness “heat-map” is shown (lower image) (C).
to conventional OCT (43). Similar to EDI-OCT, the advantage of SS-OCT in ONHD imaging is its ability to image the complete cross-sectional area of the druse. SS-OCT provides improved resolution compared to previous imaging methodologies, such as B-scan ultrasonography. SS-OCT also provides a wide 12.0 × 9.0 mm RNFL thickness map that allows evaluation of drusen-associated RNFL thinning. Being a new technology, there are few studies evaluating the use of SS-OCT for ONHD. Sato et al (5) used SS-OCT to image 4 eyes with ONHD and demonstrated that drusen were visible as ovoid regions of low reflectivity with hyperreflective curvilinear borders (Fig. 4).

**CONCLUSIONS**

New imaging technologies, such as EDI-OCT and SS-OCT, provide a means to quantify optic disc drusen dimensions and examine the integrity of neighboring structures in the retina and optic disc. These devices therefore provide the potential to develop better understanding of the relationships between disc drusen, RNFL loss, and visual field defects. They also provide a means to allow longitudinal assessment of drusen and may help explain disease mechanisms. Further research using EDI-OCT and SS-OCT may identify risk factors associated with drusen-related visual field loss and help provide prognostic information. Although there are presently no known treatments for drusen-related field loss, improved understanding of the mechanism of neuronal damage through enhanced imaging may lead to developments in this area (44).

**REFERENCES**


The North American Neuro-Ophthalmology Society, in conjunction with the American Academy of Ophthalmology, established the annual Hoyt Lecture in 2001 in honor of William Fletcher Hoyt, MD, whose contributions to neuro-ophthalmology have spanned seven decades. A fellow of Frank Walsh, MD, the grandfather of clinical neuro-ophthalmology, Dr. Hoyt co-authored the 3rd edition of Clinical Neuro-Ophthalmology, the “bible” of our specialty. A faculty member of the departments of Ophthalmology, Neurology and Neurosurgery at the University of California San Francisco since 1958, Dr. Hoyt is world-renowned as a clinician, scholar and educator. He has published more than 300 scientific contributions and has trained more than 100 fellows, many of whom are senior professors in their own right, training the next generations of neuro-ophthalmologists on six continents.

The 12th Hoyt Lecturer is Nancy J. Newman, MD, the LeoDelle Jolley Professor of Ophthalmology, Professor of Ophthalmology, Neurology and Instructor in Neurological Surgery at Emory University School of Medicine, where she serves as Director of Neuro-Ophthalmology. Dr. Newman attended Princeton University, the University of London on a Marshall Scholarship, and Harvard Medical School. She trained in Neurology at the Massachusetts General Hospital and in Neuro-Ophthalmology under the tutelage of Dr. Simmons Lessell at the Massachusetts Eye and Ear Infirmary. She serves on the Editorial Board of the American Journal of Ophthalmology, the Journal of the Neurological Sciences and the Journal of Neuro-Ophthalmology, and is a reviewer for more than 30 journals. She has over 350 publications, including co-editor of Walsh and Hoyt’s Clinical Neuro-Ophthalmology, 5th and 6th Editions. For 14 years, she was a Trustee of Princeton University and is currently the President of the Princeton University Alumni Association. At the time of this Lecture, Dr. Newman was President-Elect of the North American Neuro-Ophthalmology Society.

The 12th Hoyt Lecture: Neuro-Ophthalmology in Review: Around the Brain With 50 Fellows

Nancy J. Newman, MD

doi: 10.1097/WNO.0000000000000124

No matter what their ultimate specialty, every ophthalmologist needs to master the basics of neuro-ophthalmology. To that end, we must ensure that we continue to train effective teachers of neuro-ophthalmology. This is William F. Hoyt’s most important lasting legacy and charge. In this same spirit, Emory Neuro-Ophthalmology has tried to carry on this essential mission of training the next generations of neuro-ophthalmologists around the world not only as clinical practitioners of the art but also as academicians and teachers in their own right, contributing greatly to our specialty and, at the same time, teaching non–neuro-ophthalmologists the basics of what they need to know about neuro-ophthalmology and creating the next generation of neuro-ophthalmologists.

Through the projects and key publications of 50 Emory fellows, this neuroanatomical tour reviews advances in neuro-
ophthalmology over the past 25 years, highlighting common and uncommon disorders affecting the afferent and efferent visual systems. We begin our tour in the eye and how findings in the retina can reflect neurologic disease such as acute posterior multifocal placoid pigment epitheliopathy, carotid–cavernous fistula, cat scratch encephalopathy, and mitochondrial disease, but not migraine. We then move to the optic nerve and contributions to our understanding of optic neuropathies including optic neuritis, its demographics and treatment, anterior ischemic optic neuropathy of the young and in patients with giant cell arteritis, Leber hereditary optic neuropathy, dominant optic atrophy, the risk factors for visual loss from papilledema in patients with idiopathic intracranial hypertension, and the recently appreciated myriad of neuroimaging findings in patients with elevated intracranial pressure. Regarding the retrochiasmal pathways, publications have advanced our understanding of homonymous hemianopias, their detection, causes, congruity, and prognosis for recovery. Studies of cranial nerves 3, 4, and 6 have alerted us to the problems of radiologically unreported aneurysms and dural fistulae, the difficulties in surgically correcting residual ocular misalignment, and the prevalence of these disorders among hundreds of victims of head trauma. A study of visual complaints in patients with Parkinson disease helped neurologists understand that the most frequent causes of visual disability are ocular and potentially quite treatable. Regarding recent technology, we have written on optical coherence tomography and, most prolifically, on the uses of nonmydriatic ocular fundus photography in various settings, including the emergency department, the pediatric ophthalmology clinic, on the iphone through telemedicine, and in the classroom for teaching medical students. Fellows trained at Emory are now scattered across the globe (Fig. 1), but they remain a close-knit family of clinicians, scholars, researchers, and educators. A video of the 12th Hoyt lecture is available online within the Neuro-Ophthalmology Virtual Education Library at http://content.lib.utah.edu/cdm/ref/collection/EHSL-NOVEL/id/2051.

FIG. 1. Current location of 50 former Emory neuro-ophthalmology fellows.
We developed a novel strategy for treatment of Leber hereditary optic neuropathy (LHON) caused by a mutation in the nicotinamide adenine dinucleotide dehydrogenase subunit IV (ND4) mitochondrial gene.

**Objective:** To demonstrate the safety and effects of the gene therapy vector to be used in a proposed gene therapy clinical trial.

**Design and Setting:** In a series of laboratory experiments, we modified the mitochondrial ND4 subunit of complex I in the nuclear genetic code for import into mitochondria. The protein was targeted into the organelle by agency of a targeting sequence (allotopic expression). The gene was packaged into adeno-associated viral vectors (AAVs) and then vitreally injected into rodent, nonhuman primate, and ex vivo human eyes that underwent testing for expression and integration by immunohistochemical analysis and blue native polyacrylamide gel electrophoresis. During serial follow-up, the animal eyes underwent fundus photography, optical coherence tomography, and multifocal or pattern electroretinography. We tested for rescue of visual loss in rodent eyes also injected with a mutant G11778A ND4 homolog responsible for most cases of LHON.

**Exposure:** Ocular infection with recombinant AAVVs containing a wild-type allotopic human ND4 gene.

**Main Outcomes and Measures:** Expression of human ND4 and rescue of optic neuropathy induced by mutant human ND4.

**Results:** We found human ND4 expressed in almost all mouse retinal ganglion cells by 1 week after injection and ND4 integrated into the mouse complex I. In rodent eyes also injected with a mutant allotopic ND4, wild-type allotopic ND4 prevented defective adenosine triphosphate synthesis, suppressed visual loss, reduced apoptosis of retinal ganglion cells, and prevented demise of axons in the optic nerve. Injection of ND4 in the ex vivo human eye resulted in expression in most retinal ganglion cells. Primates undergoing vitreal injection with the ND4 test article and followed up for 3 months had no serious adverse reactions.

**Conclusions and Relevance:** Expression of our allotopic ND4 vector in the ex vivo human eye, safety of the test article, rescue of the LHON mouse model, and the severe irreversible loss of visual function in LHON support clinical testing with mutated G11778A mitochondrial DNA in our patients.

Most patients with Leber hereditary optic neuropathy (LHON) carry the G11778A mutation, which affects the nicotinamide adenine dinucleotide dehydrogenase subunit IV (ND4) gene. The authors packaged “normal” and “mutant” human ND4 genes into an adeno-associated viral vector (AAVV). Either normal ND4 AAVV or control AAVV was injected intravitreally in mouse eyes. Three days later, the mutant ND4 AAVV, which has been shown to cause an optic neuropathy in mice similar to LHON, was injected. Rhesus monkeys underwent injection of control AAVV. Two enucleated human received injections of normal ND4 AAVV.

Mouse and human eyes showed human ND4 expression in nearly all retinal ganglion cells within a week. Mouse eyes preinjected with normal ND4 AAVV maintained significantly better pattern electroretinogram amplitudes, retinal nerve fiber layer, and adenosine triphosphate synthesis than eyes preinjected with control AAVV. No complications occurred from control AAVV in primate eyes except a mild vitritis at 1 month. We may be on the cusp of a gene therapy clinical trial for LHON! These viral vectors can deliver the normal genes to retinal ganglion cells leading to production of normal ND4. Treated eyes maintained structural and functional integrity compared with vehicle eyes in this mouse model of LHON. Finally, the viral vector vehicle seemed safe in primate eyes. Although nearly all patients with unilateral LHON develop visual loss in the fellow eye within 1 year, we would only need relatively few patients to show efficacy but assessing safety may require many more.

—Michael S. Lee, MD

This article describes all the steps that have been taken in animal studies and ex vivo human eyes demonstrating the efficacy of this genetic therapy. No important adverse effects were seen in these animals. The work described should be the justification for proceeding with a phase 1 clinical trial in humans with LHON. Positive results would have more widespread beneficial implications for other diseases with mitochondrial inheritance.

—Mark L. Moster, MD

**Objective:** To evaluate Bacille Calmette-Guérin (BCG) effects after clinically isolated syndromes (CIS).

**Methods:** In a double-blind, placebo-controlled trial, participants were randomly assigned to receive BCG or placebo and monitored monthly with brain MRI (6 scans). Both groups then entered a preplanned phase with IM interferon β-1a for 12 months. From month 18 onward, the patients took the disease-modifying therapies (DMTs) that their neurologist considered indicated in an open-label extension phase lasting up to 60 months.

**Results:** Of 82 randomized subjects, 73 completed the study (33 vaccinated and 40 placebo). During the initial 6 months, the number of cumulative lesions was significantly lower in vaccinated people. The relative risks were 0.541 (95% confidence interval [CI], 0.308–0.956; \( P = 0.03 \)) for gadolinium-enhancing lesions (the primary end-point), 0.364 (95% CI, 0.207–0.639; \( P = 0.001 \)) for new and enlarging T2-hyperintense lesions, and 0.149 (95% CI, 0.046–0.416; \( P = 0.001 \)) for new T1-hypointense lesions. The number of total T1-hypointense lesions was lower in the BCG group at months 6, 12, and 18; mean changes from baseline were \(-0.09 \pm 0.72\) vs. \(0.75 \pm 1.81\) (\( P = 0.01\)), \(0.0 \pm 0.83\) vs. \(0.88 \pm 2.21\) (\( P = 0.08\)), and \(-0.21 \pm 1.03\) vs. \(1.00 \pm 2.49\) (\( P = 0.02\)), respectively. After 60 months, the cumulative probability of clinically definite multiple sclerosis was lower in the BCG + DMT arm (hazard ratio = 0.52; 95% CI, 0.27–0.99; \( P < 0.05\)), and more vaccinated people remained DMT-free (odds ratio = 0.20; 95% CI, 0.04–0.93; \( P = 0.04\)).

**Conclusions:** Early BCG may benefit CIS and affect its long-term course.

**Classification of Evidence:** BCG, as compared with placebo, was associated with significantly reduced development of gadolinium-enhancing lesions in people with CIS for a 6-month period before starting immunomodulating therapy (Class I evidence).

This study of 1 dose of Bacille Calmette-Guérin (BCG) in addition to subsequent disease modifying therapy in patients with clinically isolated syndrome (CIS) found a decrease in active magnetic resonance imaging (MRI) lesions and in subsequent clinical exacerbations. All MRI parameters (gadolinium enhancing T1, T2, and T1 hypointense) were better in patients receiving BCG. The number of exacerbations and the rate of conversion to clinically definite MS over 5 years were decreased as well.

Although this study provides Class I evidence, having been a randomized double-blind placebo-controlled trial, there are limitations as pointed out by the authors and an accompanying editorial (1). First, the sample size was small. Second, only the first portion of the clinical trial was controlled with care after 18 months in the hands of the treating neurologists.

Both the authors and editorial writers speculate on what mechanisms may be at play in the immune response to BCG that might provide the clinical benefits seen. If these results are borne out in future studies, BCG will provide a very reasonably priced, reasonably safe, and quite easily tolerated adjunctive treatment for patients with CIS and possibly for patients with clinically definite MS as well.

—Mark L. Moster, MD

I would like to point out that patients received BCG at baseline and did not start intramuscular interferon β-1a until 6 months. The difference in MRI findings between vaccinated and placebo groups was significant at 6 months and at 18 months, and this suggests a real effect of the BCG on these patients.

At 18 months, the article describes the open label extension as “unblinded.” I do not know if that means that the investigators, neuroradiologists, and patients were given the treatment allocation. That may make the 60-month data more difficult to trust because of bias. Finally, BCG vaccination gives a fairly characteristic scar and would likely leave unblinded those “in the know.”

—Michael S. Lee, MD

**REFERENCE**


**Objective:** Downbeat nystagmus (DBN) is the most frequent form of acquired persisting fixation nystagmus with different symptoms such as unsteadiness of gait, postural instability, and blurred vision with reduced visual acuity (VA) and oscillopsia. However, different symptomatic therapeutic principles are required, such as 3,4-diaminopyridine and 4-aminopyridine, that effectively suppress DBN. Chlorzoxazone (CHZ) is a nonselective activator of small conductance calcium-activated potassium (SK) channels that modifies the activity of cerebellar Purkinje cells. We evaluated the effects of this agent on DBN in an observational proof-of-concept pilot study.

**Methods:** Ten patients received CHZ 500 mg 3 times a day for 1 or 2 weeks. Slow-phase velocity of DBN, VA, postural sway, and the drug’s side effects were evaluated. Recordings were conducted at baseline, 90 minutes after first administration, and after 1 or 2 weeks.

**Results:** Mean slow-phase velocity significantly decreased from a baseline of \(2.74 \pm 2.00 \)°/s to \(2.29 \pm 2.12 \)°/s (mean ± SD) 90 minutes after first administration and to \(2.04 \pm 2.24 \)°/s (\( P < 0.001\); post hoc both \( P = 0.024\)) after long-term treatment. VA significantly increased, and postural sway in posturography showed a tendency to decrease on medication. Fifty percent of patients did not report any side effects. The most common reported side effect was abdominal discomfort and dizziness.
Conclusions: The treatment with the SK-channel activator CHZ is a potentially new therapeutic agent for the symptomatic treatment of DBN.

Classification of Evidence: This study provides Class IV evidence that CHZ 500 mg 3 times daily may improve eye movements and visual fixation in patients with DBN.

The authors gave chlorzoxazone (CHZ) 500 mg 3 times daily to 10 patients with downbeat nystagmus (DBN). They measured slow phase velocity (SPV), visual acuity (VA), and postural sway at baseline and after 1-2 weeks of treatment. They found a mean improvement of 44% in SPV, a marginal change in VA, and no change in postural sway. Fifty percent developed abdominal discomfort and dizziness.

There is no definitive treatment for DBN, but the aminopyridines, 4-aminopyridine (4-AP), and 3,4-diaminopyridine (3,4-DAP), seem to work the best in many patients. Unfortunately, 3,4-DAP is not commercially available in the United States. Although 4-AP is available, it is hard to come by and costs can be more than 1,000 dollars per month. For patients with DBN who cannot get or afford 4-AP, CHZ may represent another reasonable therapeutic alternative. This study included a very small group of patients, and time will tell if this is truly helpful and whether an alternative dosing schedule could improve outcomes in DBN.

—Michael S. Lee, MD

A new nystagmus treatment is always welcome, especially one reasonably priced and widely available (CHZ is commonly known in the United States as parafon forte, a muscle relaxant). What is hard to glean from this article, but of utmost importance, is whether the responders felt any symptomatic improvement. The bellyache side effect is not worth it if it does not provide much relief.

—Mark L. Moster, MD


Importance: Children with optic pathway gliomas (OPGs) frequently experience vision loss from their tumors. Standard frontline treatment using carboplatin-based chemotherapy typically produces only a modest benefit (e.g., stabilization or 0.2 logMAR improvement) in visual acuity (VA). Bevacizumab is a monoclonal antibody that targets vascular endothelial growth factor and acts primarily as an anti-angiogenic agent. Recent reports suggest a qualitative improvement in vision after bevacizumab-based treatment in children with OPGs.

Observations: We report 4 cases of pediatric OPGs (2 neurofibromatosis Type 1-related and 2 sporadic cases) that received treatment with bevacizumab due to progressive VA or visual field (VF) loss despite prior treatment with chemotherapy or proton-beam radiation. All 4 subjects demonstrated a marked improvement in their VA, VF, or both while receiving bevacizumab-based therapy. Three patients had complete resolution of their VA or VF loss in at least 1 eye, 2 of whom had previously received bevacizumab therapy.

Conclusions and Relevance: Given that most patients with OPG-related visual impairment will show modest or no visual improvement with standard treatment, the incorporation of bevacizumab in these cases may greatly improve visual outcomes and should be considered in appropriate clinical situations.

Although an anecdotal report of 4 patients, this article demonstrates hope for visual recovery in children with optic glioma and progressive visual loss or radiographic enlargement. Particularly encouraging is that the improvement was also seen in 3 children with prior bevacizumab treatment.

Two patients had radiation therapy 4 and 7 months before visual deterioration, so it is difficult to distinguish the cause of the deterioration between tumor progression and radiation toxicity. This raises the possibility that IV bevacizumab may benefit patients with radiation toxicity. However, this possibility should be considered in view of conflicting reports that bevacizumab may actually contribute to optic neuropathy in the setting of radiation (1).

For time being, it is likely reasonable to try bevacizumab in a child with progressive visual loss from glioma. Where this treatment ultimately fits in the global treatment of these patients awaits further clinical trials.

—Mark L. Moster, MD

I think it is unlikely that these 2 patients had radiation injury. One patient presented at 7 months but began to lose vision at 4 months after radiation. Radiation injury typically does not occur this early in the clinical course. The other patient was treated with radiation 4 months prior, because she was losing vision and this was likely progression of that visual loss.

In 3 patients, there was new and progressive visual loss (the fourth was asymptomatic, so we do not know the time course). I wonder if the previous bevacizumab therapy was ineffective because there was no active growth of the gliomas; whereas the marked recovery of vision with the current treatment of bevacizumab occurred, because the authors treated at an acute stage of growth.

—Michael S. Lee, MD

REFERENCE


Purpose: To investigate retrograde axonal degeneration for its potential to cause microcystic macular edema (MME), a maculopathy that has been previously described in patients with demyelinating disease. To identify risk factors for MME and to expand the anatomic knowledge on MME.

Design: Retrospective case series.

Participants: We included 117 consecutive patients and 180 eyes with confirmed optic neuropathy of variable etiology. Patients with glaucoma were excluded.

Methods: We determined age, sex, visual acuity, etiology of optic neuropathy, and the temporal and spatial characteristics of MME. Eyes with MME were compared with eyes with optic neuropathy alone and to healthy fellow eyes. With retinal layer segmentation, we quantitatively measured the intraretinal anatomy.

Main Outcome Measures: Demographic data, distribution of MME in the retina, and thickness of retinal layers were analyzed.

Results: We found MME in 16 eyes (8.8%) from 9 patients, none of whom had multiple sclerosis or neuromyelitis optica. The MME was restricted to the inner nuclear layer (INL) and had a characteristic perifoveal circular distribution. Compared with healthy controls, MME was associated with significant thinning of the ganglion cell layer and nerve fiber layer, as well as a thickening of the INL and the deeper retinal layers. Youth is a significant risk factor for MME.

Conclusions: MME is not specific for demyelinating disease. It is a sign of optic neuropathy irrespective of its etiology. The distinctive intraretinal anatomy suggests that MME is caused by retrograde degeneration of the inner retinal layers, resulting in impaired fluid resorption in the macula.

In this retrospective study, the authors searched their databases for patients with a history of optic neuropathy who underwent macular optical coherence tomography testing. They found that 16 of 180 eyes had microcystic macular edema (MME) limited to the inner nuclear layer. A striking finding was the perifoveal location of the MME in all eyes. The cause of the optic neuropathy ranged from compressive (n = 9), vascular (n = 3), hereditary (n = 2), and idiopathic (n = 2), and the proportions did not differ from the non-MME eyes. The shortest time to develop MME was 4 months and the longest time was several years. The authors make a compelling argument that this represents a retrograde degenerative process.

I actually have seen these changes on optical coherence tomography in patients with optic neuropathy, but did not associate the findings. I had assumed that the patient had developed cystic retinal changes and made a referral to a retinal specialist. Now I know. It has a pretty characteristic appearance, and I would recommend the reader look at the images.

—Michael S. Lee, MD

This article demonstrates that MME is not likely part of the pathophysiologic process of inflammatory optic neuropathy as previously proposed (first for multiple sclerosis [MS] and then for neuromyelitis optica [NMO]), but a nonspecific secondary change occurring in optic neuropathy. It was seen in compressive, vascular, and hereditary causes of optic neuropathy but further clinical details on these patients were not provided. If it were part of the primary inflammatory process in optic neuritis from MS or NMO, one would not expect to see it in these other optic neuropathies.

The authors excluded glaucoma cases “to better match patients with MS in whom MME had been first described...” I do not understand how ischemic, compressive, and hereditary optic neuropathy are better matches for patients with MS, but that does not detract from the findings in this study. Indeed, MME has now been described in a group of glaucoma patients (1). I agree with Michael that a few years ago, I would send a patient with MME for retinal consultation, but am now comfortable that it is part of the process affecting the optic nerve.

—Mark L. Moster, MD

REFERENCE


Objective: To evaluate clinical features among patients with neuromyelitis optica spectrum disorders (NMOSD) who have myelin oligodendrocyte glycoprotein (MOG) antibodies, aquaporin04 (AQP4) antibodies, or seronegativity for both antibodies.

Methods: Sera from patients diagnosed with NMOSD in 1 of 3 centers (2 sites in Brazil and 1 site in Japan) were tested for MOG and AQP4 antibodies using cell-based assays with live transfected cells.

Results: Among the 215 patients with NMOSD, 7.4% (16/215) were positive for MOG antibodies and 64.7% (139/215) were positive for AQP4 antibodies. No patients were positive for both antibodies. Patients with MOG antibodies represented 21.1% (16/76) of the patients negative for AQP4 antibodies. Compared with patients with AQP4 antibodies or patients who were seronegative, patients with MOG antibodies were more frequently male, had a more restricted phenotype (optic nerve more than spinal cord), more frequently had bilateral simultaneous optic neuritis, more often had a single attack, had spinal cord lesions distributed in the lower portion of the spinal cord, and usually demonstrated better functional recovery after an attack.

Conclusions: Patients with NMOSD with MOG antibodies have distinct clinical features seronegative for both antibodies.
Myelin oligodendrocyte glycoprotein (MOG) antibodies have been seen in patients with numerous demyelinating disorders, such as acute disseminated encephalomyelitis, MS, and adrenoleukodystrophy. This study evaluated MOG antibodies and aquaporin04 (AQP4) antibodies in patients with neuromyelitis optica spectrum disorders (NMOSD). The findings are interesting in that the clinical features were somewhat different for those with MOG, AQP4 or those that were seronegative for both. No patients had both MOG and AQP4 antibodies. Patients who met the diagnostic criteria for definite NMO rarely had MOG antibodies (1/101), whereas 84% (85/101) had AQP4 antibodies. The other variants in the spectrum of NMOSD include longitudinal extensive transverse myelitis (LETM) or bilateral simultaneous or recurrent optic neuritis. LETM patients had MOG antibody 6.4% of the time but the optic neuritis group had the highest association, being positive for MOG antibody 27.8% of the time (10/36) with only 30.5% positive for AQP4. Other features associated with MOG antibody was a more likelihood of being male, having better recovery, and having a single rather than multiple attacks. What we do not really know is if these patients are more likely behaving in a better prognostic fashion because they really do have early MS instead of NMO, and their future clinical course and MRI picture will establish this as time goes on. Nonetheless, just as finding AQP4 antibody has improved our understanding and treatment of a subset of optic neuritis patients, finding other associated antibodies may further refine our diagnostic and therapeutic capabilities.

—Mark L. Moster, MD

Patients with recurrent or bilateral simultaneous optic neuritis could develop NMO. Based on this article, if the MOG antibody is positive, this indicates a better visual prognosis than those who are NMO positive or seronegative for both. The visual acuity was <20/200 in 19%, 73%, and 47% of MOG positive, NMO positive, and seronegative patients, respectively. It may be helpful to order this test for prognostic purposes.

—Michael S. Lee, MD