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OCT and NMO: Are There Methods to Our Madness?

Laura J. Balcer, MD, MSCE, Steven L. Galetta, MD

The distinction between typical acute demyelinating optic neuritis (ON), as may occur during the course of multiple sclerosis (MS), and ON in the setting of neuromyelitis optica (NMO) is a challenge frequently faced by neuro-ophthalmologists. The separation of these 2 forms of ON is important based on the relatively poor visual prognosis associated with NMO and the differences in how these 2 conditions are treated (1–4). Patients with NMO often require immunosuppressive therapy and interferon-beta may have deleterious effects on the relapse rate in NMO patients (1,2). Although the aquaporin-4 antibody continues to be evaluated as an important diagnostic NMO biomarker in both clinically definite and limited forms (NMO spectrum disorders) (5,6), there is increasing attention to the structure and function of the anterior visual pathway as a potential system for helping to distinguish patients with NMO vs MS.

Optical coherence tomography (OCT) has emerged as a powerful tool to provide structural information about the retina and optic nerve. Thus, it is logical to ask whether OCT may be able to distinguish unilateral ON associated NMO from that typically observed with MS. This question was one of many addressed by 2 independent reports (7,8) in this issue of the *Journal of Neuro-Ophthalmology*. As such, both articles compare peripapillary retinal nerve fiber layer (RNFL) thickness, measured by spectral-domain optical coherence tomography, in eyes with a history of ON for patients with NMO vs relapsing-remitting multiple sclerosis (RRMS). Consistent with findings in the literature from previous investigations of time-domain optical coherence tomography (9), eyes with a history of ON (>6 months before OCT) in both of these cross-sectional studies demonstrated thinner RNFL in patients with NMO compared with RRMS (Table 1).

Despite the similar imaging findings, the 2 studies demonstrated different results in terms of the magnitudes of the differences between NMO and RRMS eyes (effect sizes). The reader, therefore, may be left with some questions given the different statistical outcome of the 2 studies:

1. Does peripapillary RNFL thickness by OCT have a clinical role in distinguishing eyes of patients with NMO vs RRMS in the months following acute ON?
2. What factors in research design, case definition, and statistical analysis may have contributed to the observed differences (and similarities) in the findings between the 2 reports, and how can the reader apply what we learn here to future studies in which 2 investigations by established research groups yield somewhat different results?
3. What do statistical tests do (not) for us, anyway? After all, if statistics are only a tool to help us determine the role of chance in our results, then why so much emphasis on the *P*-value? What about clinical meaningfulness … or potential bias?

Systematic comparison of the 2 studies with regard to methodologies actually shows that they are more similar than different with regard to the underlying results, and with respect to the take-home message on OCT studies of ON from this issue of the *Journal*. Several methodologic aspects of these studies are important to highlight here, particularly given their broader applicability to neuro-ophthalmologic studies in general.
1. One eye or 2? In the case of unilateral ON, the affected eye is usually the one of primary interest. However, to the extent that the fellow eye may help to estimate a “baseline” RNFL thickness in patients with ON as a first demyelinating event, or could demonstrate evidence of subclinical RNFL axonal loss in MS cohorts, investigators often choose to include both eyes of each patient. Including both eyes, if appropriate for the research question, increases statistical power and allows for data from affected (history of ON) eyes and those without ON history. Both the study by Lange et al (7) and that by Bichuetti et al (8) compared affected eyes primarily using pairwise comparisons of NMO vs RRMS groups. Lange et al (7) also calculated intereye differences and found these to be the most significant discriminator of NMO vs RRMS eyes. Although these authors used statistical models to examine potential associations of RNFL thinning and clinical features, such as worse Expanded Disability Status Scale (EDSS) score, other statistical techniques, such as linear mixed effects or generalized estimating equation (GEE) models, could also be used to determine whether NMO vs RRMS status could be associated with RNFL thinning, accounting for within-patient intereye correlations and potentially including both eyes in patients with bilateral ON. The advantage of using a GEE regression approach is that if the eyes of patients are very different, then the models will adjust the variances of the observations to reflect the intercorrelation of the eyes. Such models will yield results similar to simple linear regression. If, however, the eyes of patients tend to be more similar than different (i.e., intercorrelated), then the variances will be adjusted so that the levels of significance of associations between variables reflect these similarities of the eyes within patients. The use of models that include this approach is therefore a win–win for study designs and analyses that include both eyes of each patient—and including both eyes when possible is a double win–win from a generalizability standpoint.

2. Statistical tests: how do we choose? The choice of statistical tests is based on characteristics of the study design, variables, and outcome measures (10). Since the study design depends, by definition, on the research question, it is at this phase of the research process that the types of statistical tests should be first considered. Methods for descriptive statistics (calculation of summary measures, such as mean) and hypothesis testing (comparison of groups or measurement of associations) are both dependent upon the distributions of observations as judged by the investigator (do the data fit a normal distribution or “bell” curve, for example?). When continuous data fit assumptions for normality, including absence of skewness and relatively large sample size, then summary measures of mean and standard deviation and hypothesis tests of linear regression, t tests, and analyses of variance are used. However, when small sample size (rule of thumb approximately <20 per group) or measurable skewness are evident, then nonparametric tests that are based on ranks or “order” within the data points are the preferred methods. Table 1 demonstrates the interdependence of sample size, effect size (difference in means), and statistical methods for comparison of group data in determining the outcome of comparisons of groups with respect to statistical significance. Investigators in the study by Lange et al (7) used a Wilcoxon rank sum test to compare the NMO vs RRMS eye groups with history of ON (Table 1). This seems appropriate, given the relatively modest sample size in each group (26 NMO and 13 RRMS); the result was a P-value of 0.46, indicating a 46% probability that the difference in mean RNFL thickness of ~10 µm could have been observed by chance alone in this cohort. Although neuro-ophthalmologists would consider a 10-µm difference in RNFL thickness, particularly between groups, to be clinically meaningful (~10% of normal RNFL thickness by SD OCT), the P-value of 0.46 may falsely lead the reader to believe that no real differences exist between NMO and RMS for RNFL thickness months following ON. Using a 2-sample t test, the difference in mean RNFL thickness in the study by Lange et al (7), given the same standard deviations and sample sizes, would have demonstrated a trend (P = 0.09). Also using a 2-sample t test, Bichuetti et al (8) found the difference in NMO vs RRMS eyes with a history of ON to be statistically significant (P = 0.004), although there was also a greater effect size (difference in means) and smaller overall sample size. In general, nonparametric tests, such

<table>
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<tr>
<th></th>
<th>NMO + ON</th>
<th>RRMS + ON</th>
<th>P, Statistical Test</th>
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<tbody>
<tr>
<td>Lange et al (7)</td>
<td>26</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Number of eyes (n)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>RNFL thickness, mean ± SD</td>
<td>63.69 ± 18.32</td>
<td>73.85 ± 15.20</td>
<td>P = 0.46 (Wilcoxon rank sum test)</td>
</tr>
<tr>
<td>Bichuetti et al (8)</td>
<td>8</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Number of eyes (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RNFL thickness, mean ± SD</td>
<td>65.3 ± 18.3</td>
<td>80.1 ± 14.8</td>
<td>P = 0.004 (2-sample t test)</td>
</tr>
</tbody>
</table>

NMO, neuromyelitis optica; ON, optic neuritis; RNFL, retinal nerve fiber layer; RRMS, relapsing-remitting multiple sclerosis; SD, standard deviation.

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**TABLE 1.** Retinal nerve fiber layer thickness values for eyes of patients with history of acute optic neuritis and diagnosis of neuromyelitis optica vs relapsing-remitting multiple sclerosis from 2 studies (7,8)
as the Wilcoxon rank sum test, are more conservative with regard to demonstrating statistical significance, yet may be more appropriate in the case of small sample sizes, the most common situation in which data cannot be assured to fit assumptions for normality.

3. Sample size: what goes into it? The answer is—a lot! Determining the minimum sample size, or number of patients or eyes per group needed to demonstrate a statistically significant difference between groups if one actually exists, depends on the effect size (minimum clinically meaningful difference we would like to detect), variance (or standard deviations anticipated for each group), power (1—the maximum probability of a type II error, or chance of not detecting a difference when one exists), and alpha (maximum probability of a type I error, or chance of demonstrating a significant difference when one does not, in fact, exist). Investigators generally set power at 0.80–0.90 and alpha at 0.05. Based on the observed differences in means, the standard deviations, and power of 0.80 and alpha 0.05, the numbers of patients/eyes needed to show a statistically significant difference in the study by Lange et al (7) would be 61 with NMO and 31 with RRMS. For the investigation by Bichuetti et al (8), 16 with NMO and 32 with RRMS would be needed. These numbers assume similar distributions of NMO and MS eyes to those chosen in the published studies. It turns out, however, that fewer patients are usually needed for the comparator (or control) group compared with the diseased group of interest; this is related to the relatively smaller variances observed in groups of “controls” vs cases (see next section). Although the study by Bichuetti et al (8) had the opposite design of fewer cases (NMO) than controls (RRMS), significant differences were likely demonstrated by virtue of the larger effect size and less conservative statistical test (Table 1). Larger sample sizes also minimize the effects of sampling error or the potential to observe results that do not accurately estimate the true values for measurements in the populations of interest. Statistical software packages have become user-friendly and allow investigators to calculate sample sizes using information from the literature or from their own preliminary data.

4. Might we need more patients with the disease of interest vs in the comparator group? Yes! Since the distributions of observations are generally “tighter” in control or comparator groups, with less variance and lower standard deviations (as in the RRMS groups in the 2 studies), more patients with the disease of interest may be needed than controls to show a significant difference. In some cases, disease-free controls or a comparator group of patients with a milder form of disease may be easier to recruit for studies, yet relatively fewer are required. Statistical software packages include options for specifying ratios of cases and controls when calculating sample size.

5. When do statistical models help us, and what should they include? Models such as linear and logistic regression, and GEE (allows adjustment for inter-eye correlations), are useful when examining associations between 2 or more variables or characteristics. These models enable us to account for age, for example, while determining the relation between RNFL thickness and visual function or neurologic disability. A general rule of thumb for regression and sample size is that at least 10 patients/eyes are needed per covariate in the model; for example, a regression model examining the association of RNFL thickness and EDSS score, accounting simultaneously for age, will require at least 30 patients. The question of what disease characteristics to account for in regression analyses when determining associations of 2 other variables depends on the research question. If a characteristic, such as history of ON, is part of the disease definition (as in NMO), then accounting simultaneously for that variable could lessen the observed degree of association between the primary characteristics of interest. Consulting a biostatistician when considering use of regression models can be helpful to ensure that both the data and the research question are consistent with these types of analyses.

6. Why does everyone keep asking about our inclusion criteria? … and case definition? Inclusion criteria, and specifically the case definition for disease, are critical to determining who is included in your study, and how they are categorized. In the case of disorders for which the spectrum is still being discovered and investigated, different studies may use slightly different case definitions. This is perhaps the most important area of potential difference between studies, particularly when diagnosis of a disease entity relies, even in part, upon tests that may be imperfect “gold standards.” Baseline likelihood of a disease within the population sampled also affects the predictive value of diagnostic tests; the less prevalent the disease, the greater the likelihood of false-positive test results. Differences in geographic region, genetics, and other population characteristics are likely factors in observed differences between studies that may seem otherwise similar with respect to their design, analyses, and other methodologic aspects.

7. How can we put this all together? The authors of both manuscripts are to be congratulated for taking on this challenging and critical area of research in neuro-ophthalmology. Their work further emphasizes the importance of distinguishing NMO from MS and highlights how the relatively poor prognosis in NMO may be related to the marked degrees of axonal loss that have been noted consistently across OCT studies. These investigations, when viewed from the standpoint of how methodologic differences may play a role, have yielded results that are more similar than different. So, as neuro-ophthalmologists, we probably do have methods to our madness after all!
REFERENCES
Spectral-Domain Optical Coherence Tomography of Retinal Nerve Fiber Layer Thickness in NMO Patients

Alex P. Lange, MD, Reza Sadjadi, MD, Feng Zhu, MSc, Samir Alkabie, MSc, Fiona Costello, MD, Anthony L. Traboulsee, MD

Background: Neuromyelitis optica (NMO) is a demyelinating syndrome of the central nervous system. NMO might be underdiagnosed at early stages when patients have not yet developed the full spectrum of disease. The aim of this study was to analyze the retinal nerve fiber layer (RNFL) with optical coherence tomography (OCT) and to compare RNFL measurements between NMO patients, patients with relapsing–remitting multiple sclerosis (RRMS), and healthy controls to determine whether differences in RNFL thickness could be an early diagnostic marker for NMO.

Methods: In a cross-sectional study, eyes of 25 NMO patients, 25 RRMS patients, and 50 healthy controls underwent RNFL measurements by OCT. Clinical parameters were collected by history and chart review. Pairwise Wilcoxon rank sum tests with Holm correction were used to compare means of RNFL thickness among 6 groups (NMO, RRMS, and healthy control) of patients (without or with 1 or more episode of optic neuritis [ON]). The association between RNFL thickness and patient characteristics for NMO group was examined via linear mixed-effects models (adjusting for within-patient intereye correlations and history of ON, where appropriate).

Results: Based on the pairwise Wilcoxon rank sum tests with Holm correction, significant differences were found between NMO with 1 episode of ON and non-ON eyes (mean RNFL 63.7 vs 97.0 μm, P < 0.0001), multiple sclerosis (MS) non-ON eyes, and controls (RNFL 93.2 vs 98.4 μm, P = 0.03). No significant differences were found between NMO and MS with 1 attack of ON eyes (RNFL 63.7 vs 73.9 μm, P = 0.46), NMO non-ON eyes and healthy controls (RNFL 97.0 vs 98.4 μm, P = 0.56), and NMO non-ON and MS non-ON (RNFL 97.0 vs 93.2 μm, P = 0.56). For NMO group, RNFL thickness was associated with a history of ON (P < 0.001) but not with disability or disease duration when adjusting for the history of ON (P > 0.1).

Conclusions: RNFL in NMO is not different enough to distinguish NMO ON from MS ON eyes, but the intereye difference in RNFL with a history of unilateral ON may be a better diagnostic marker for NMO.
Patients and Methods:

Study Design

This was a cross-sectional cohort study. The British Columbia MS (BCMS) database was used to help identify eligible NMO patients. The database has longitudinally collated clinical information on MS and NMO patients registered with 1 of 4 MS clinics across British Columbia since 1980 and is estimated to include 80% of MS and NMO patients in British Columbia (10,11).

Patient Population

Patients were recruited between August 2009 and March 2011. Subjects with NMO spectrum disorder were identified from the BCMS database and were invited to participate by letter. If no answer was received within 4 months, a second invitation letter was sent. All patients were diagnosed by an experienced MS neurologist with special interest in NMO.

Inclusion criteria for NMO spectrum disorders were as follows:

1. NMO Diagnostic Criteria positive—fulfill criteria published in 2006 (5).
2. NMO Diagnostic Criteria negative—NMO-IgG antibody present with either severe ON or severe TM and clinically suspected NMO (patients with either bilateral simultaneous ON or TM plus normal brain magnetic resonance imaging [MRI] and contiguous spinal cord lesions over at least 3 segments) (12).

Patients with RRMS, based on the modified McDonald criteria (13), and healthy controls were recruited from the University of British Columbia Hospital MS clinic, accompanying persons and hospital staff. We aimed to match for age (±5 years) and refraction (±2 diopters).

Exclusion criteria included patients with a recent history of ON (≤6 months), history of ocular disease (including macular degeneration, diabetic retinopathy, uveitis, and glaucoma), history of diseases that could mimic MS or NMO, neurodegenerative conditions that could impact OCT testing (Parkinson disease, Alzheimer disease), and subjects with difficulty maintaining fixation and/or myopic refraction of more than −5.0 diopters. Exclusion criteria were the same for controls as for NMO and MS patients.

This study was approved by the Clinical Research Ethics Board at the University of British Columbia. A patient information sheet was provided, and informed consent was obtained before subject enrolment in the study.

Clinical Assessment

Clinical and demographic data were obtained from the BCMS database, supplemented by chart review, structured questionnaires, and history taking by the study physician (AL). Information collected included age, sex, date of symptom onset, history and number of ON events, use of any immunomodulatory drugs (IMDs) or other medications, presence of co-morbidities, MRI findings (all read by a masked radiologist with expertise in NMO and MS), and current Expanded Disability Status Scale (EDSS) scores. If the EDSS score was not recent (within 6 months) or if new MS symptoms were reported, an EDSS examination was performed by an MS neurologist (R.S. or A.T.) at the time of the OCT testing. NMO antibodies were tested in our own laboratory and in at least one other laboratory using ELISA-based techniques (Mayo Laboratories, Rochester, MN; Calgary Mitogen Laboratory, Calgary, Canada) or cell-based techniques (Tohoku Laboratory, Sendai, Japan). If 1 result was positive, antibody status was rated as positive. To minimize misdiagnosis of the antibody-negative cohort, these cases were independently reviewed by 2 other physicians.

Spectral-Domain Optical Coherence Tomography Testing

All cases and controls were assessed by a neuro-ophthalmologist specialized in spectral-domain optical coherence tomography (SD-OCT) (A.L.), using the RNFL protocol of Heidelberg Spectralis SD-OCT (Software version 5.1.2; Heidelberg Engineering, Heidelberg, Germany) in high-resolution mode (axial resolution 3.8 μm, 19,000 scans per second). Sixteen consecutive circular B-scans (each composed of 1,536 A-scans) with a diameter of 3.4 mm were automatically averaged to reduce speckle noise. The online tracking system compensated for eye movements. Several scans were taken without pupil dilation, with the best centered with a quality of at least 25 (14) chosen for analysis. The software algorithm provided objective refraction (spherical equivalent) and the RNFL thickness for the temporal, superior, nasal, and inferior quadrants and the overall mean of these quadrants.

Statistical Analysis

Pairwise Wilcoxon rank sum tests with Holm correction were used to compare RNFL thickness among 6 groups (NMO, RRMS, and healthy control) of patients (without or with 1 or more history of ON). These were performed separately for NMO or RRMS ON eyes and non-ON eyes.

For NMO patients, Spearman rank correlation and Pearson correlation were used to examine the association between RNFL thickness and disability (EDSS) and between RNFL thickness and disease duration, respectively. These were performed for all NMO eyes and then separately for NMO ON eyes and non-ON eyes. Furthermore, a linear mixed-effects model was developed to examine the association between RNFL thickness and patient characteristics,
which include sex, current age, disease duration, disability (EDSS) (grouped as: <2, 2.5, 3, 3.5, 4, ≥4.5), history of ON (present, absent), refraction, use of current IMD (ever, never), ethnicity (Asian/Caucasian), and NMO diagnostic criteria positive/negative status, while adjusting for within-patient intereye correlations (i.e., 2 eyes from the same person are correlated). The association between RNFL thickness and patient characteristics initially was assessed univariately. If considered clinically important (i.e., the EDSS) or statistically significant (disease duration) from the univariate analysis, then the model was also adjusted for the history of ON (ever, never). Complementary analyses were performed for each quadrant of the overall RNFL thickness (inferior, superior, temporal, and nasal). Statistical analyses were performed using R: A Language and Environment for Statistical Computing V.2.13.2 (R Foundation for Statistical Computing, Vienna, Austria; 2011).

**Main Outcomes**

The primary outcome measures were RNFL thickness in NMO patients, RRMS patients, and healthy controls. Secondary outcomes measures were correlation between RNFL in NMO eyes, EDSS, and disease duration. Furthermore, RNFL values in unilateral ON eyes were compared between the NMO and the RRMS groups.

**RESULTS**

**Patient Demographics and Clinical Characteristics**

An invitation letter was sent to 40 NMO patients. Twenty positive responses were received after first contact and an additional 7 after second recruitment letter. These 27 patients with NMO spectrum disorder initially consented and underwent SD-OCT. However, 2 NMO patients had to be excluded due to high myopic refraction (more than −5.0 diopters), leaving 25 patients in the NMO group. Twenty-five gender-, age-, and EDSS-matched patients with RRMS, according to the modified McDonald criteria (13) and 50 healthy controls were included. A demographic summary of our study patients is given in Table 1.

**TABLE 1.** Demographic data of neuromyelitis optica and multiple sclerosis patients and controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NMO</th>
<th>MS</th>
<th>Control</th>
<th>P</th>
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<tbody>
<tr>
<td>Number of Subjects</td>
<td>25</td>
<td>25</td>
<td>50</td>
<td></td>
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<tr>
<td>Mean age (±SD) (years)</td>
<td>49.60 (±12.94)</td>
<td>43.5 (±9.1)</td>
<td>49.2 (±10.2)</td>
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<td>Gender, F:M</td>
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<td>23:2</td>
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</tr>
<tr>
<td>Mean RNFL SD-OCT (±SD) (μm)</td>
<td>74.12 (±23.20) (50 eyes)</td>
<td>88.16 (±16.81) (50 eyes)</td>
<td>98.44 (±8.81) (100 eyes)</td>
<td></td>
</tr>
<tr>
<td>Refraction (±SD) (diopters)</td>
<td>−1.08 (±2.10) (50 eyes)</td>
<td>−1.32 (±2.68) (50 eyes)</td>
<td>−0.34 (±1.73) (100 eyes)</td>
<td></td>
</tr>
<tr>
<td>Median EDSS (range)</td>
<td>2.50 (0.0–8.0)</td>
<td>2.50 (1.0–6.5)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Mean disease duration (±SD) (years)</td>
<td>7.64 (±4.73)</td>
<td>12.11 (±8.30)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>On disease modifying therapy (%)</td>
<td>68</td>
<td>44</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

EDSS, expanded disability status scale; F, female; M, male; MS, multiple sclerosis; NMO, neuromyelitis optica; RNFL, retinal nerve fiber layer; SD, standard deviation; SD-OCT, spectral domain optical coherence tomography.

The 3 groups were broadly similar for age and refraction, although differed by disease duration (NMO disease duration shorter than MS) and by gender (with more men included in the control group). Fifteen of the 25 NMO patients fulfilled the NMO diagnostic criteria and 10 patients met our additional criteria for NMO spectrum disorder (3 with pos IgG and ON; 3 with positive IgG and TM; 2 with bilateral simultaneous ON, normal brain MRI and spinal cord lesions; and 2 with TM, normal brain MRI, and spinal cord lesions).

Five patients (10 eyes) had no previous history of ON, 11 (22 eyes) had a history of bilateral ON, and 9 (18 eyes) had a history of unilateral ON. In the ON group, there were 5 eyes affected by 2 or more ON events, whereas the remaining eyes (n = 26) were affected by a single ON event. Twenty patients had a history of TM. Eight patients who fulfilled NMO diagnostic criteria had positive NMO-IgG titers, 6 were tested negative, and 1 patient was not tested. In the negative group, 6 were tested IgG positive and 4 were negative. Twenty-two patients had MRI spine findings consistent with NMO (spinal cord lesion >3 segments).

In the MS group, 17 patients had no history of ON, 5 had a history of bilateral sequential ON, and 3 had a history of unilateral ON. Thus, 13 eyes (26%) were previously affected by single ON. None of the eyes had a history of 2 or more ON events.

**Main Outcomes**

The overall and different quadrant RNFL values of different groups are shown in Table 2. P-values between different groups are shown in Table 2, NMO eyes with history of 1 ON event had 34% lower RNFL thickness compared with NMO non-ON eyes (P < 0.0001). The mean intereye difference in the RNFL thickness (non-ON eyes–ON eyes) for NMO patients with unilateral ON was 36.3 μm (SD ±19.45 μm, P = 0.005) and 16.7 μm (SD ±17.0 μm, P = 0.25) for MS eyes with unilateral ON (Wilcoxon signed rank test). Mean RNFL values in NMO ON eyes tended to be thinner compared with MS ON eyes, but the difference was not statistically significant (P = 0.46). Mean RNFL values in NMO non-ON eyes were not different from healthy controls.


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TABLE 2. Overall and quadrant retinal nerve fiber layer values for neuromyelitis optica and multiple sclerosis patients and controls

<table>
<thead>
<tr>
<th>Patient Groups</th>
<th>NMO Without Optic Neuritis (N = 18)</th>
<th>NMO With 1 Optic Neuritis (N = 26)</th>
<th>NMO With &gt;1 Optic Neuritis (N = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall RNFL</td>
<td>97.00 (±11.14); 84–116</td>
<td>63.69 (±18.32); 36–94</td>
<td>50.67 (±8.09); 38–61</td>
</tr>
<tr>
<td>Quadrant measurements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temporal</td>
<td>77.39 (±11.31); 58–99</td>
<td>52.04 (±17.19); 26–96</td>
<td>47.33 (±9.50); 39–59</td>
</tr>
<tr>
<td>Inferior</td>
<td>123.83 (±17.94); 92–151</td>
<td>84.50 (±26.51); 37–128</td>
<td>60.50 (±9.07); 49–71</td>
</tr>
<tr>
<td>Nasal</td>
<td>70.61 (±13.88); 44–99</td>
<td>41.35 (±15.54); 10–74</td>
<td>32.67 (±11.89); 13–46</td>
</tr>
<tr>
<td>Superior</td>
<td>116.28 (±20.89); 52–140</td>
<td>76.42 (±25.70); 36–121</td>
<td>61.33 (±11.34); 49–76</td>
</tr>
<tr>
<td>MS Patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MS Without Optic Neuritis (N = 13)</td>
<td>93.19 (±14.41); 63–136</td>
<td>73.85 (±15.20); 50–97</td>
<td>98.44 (±8.81); 79–127</td>
</tr>
<tr>
<td>Quadrant measurements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temporal</td>
<td>68.05 (±11.88); 37–96</td>
<td>56.69 (±21.32); 29–94</td>
<td>70.98 (±11.16); 49–103</td>
</tr>
<tr>
<td>Inferior</td>
<td>120.51 (±19.72); 88–180</td>
<td>96.77 (±19.24); 57–126</td>
<td>127.38 (±14.31); 96–177</td>
</tr>
<tr>
<td>Nasal</td>
<td>74.38 (±18.29); 38–127</td>
<td>48.77 (±14.75); 27–66</td>
<td>74.00 (±12.77); 53–108</td>
</tr>
<tr>
<td>Superior</td>
<td>109.57 (±25.32); 44–173</td>
<td>93.54 (±22.94); 59–130</td>
<td>121.24 (±15.96); 91–156</td>
</tr>
</tbody>
</table>

RNFL values are associated with longer disease duration ($r = -0.34$, $P = 0.02$, Pearson correlation) when looking at the whole NMO group. No correlation was found when analysis was repeated on the NMO non-ON eyes (EDSS: $r = -0.13$, $P = 0.62$; disease duration: $r = 0.17$, $P = 0.52$) or when analysis was repeated on the NMO ON eyes (EDSS: $r = -0.33$, $P = 0.06$; disease duration: $r = -0.32$, $P = 0.07$).

TABLE 3. Statistical analysis of overall retinal nerve fiber layer thickness for neuromyelitis optica and multiple sclerosis patients and controls

<table>
<thead>
<tr>
<th>Patient Groups</th>
<th>Healthy Controls</th>
<th>$P$ value (Pairwise Wilcoxon Rank Sum Tests With Holm Correction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMO without ON (n = 18)</td>
<td>n = 100</td>
<td>0.56</td>
</tr>
<tr>
<td>97.00 (±11.14); 84–116</td>
<td>98.44 (±8.81); 79–127</td>
<td></td>
</tr>
<tr>
<td>NMO with 1 ON (n = 26)</td>
<td>Healthy controls (n = 100)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>63.69 (±18.32); 36–94</td>
<td>98.44 (±8.81); 79–127</td>
<td></td>
</tr>
<tr>
<td>NMO with &gt;1 ON (n = 6)</td>
<td>Healthy controls (n = 100)</td>
<td>0.0005</td>
</tr>
<tr>
<td>50.67 (±8.09); 38–61</td>
<td>98.44 (±8.81); 79–127</td>
<td></td>
</tr>
<tr>
<td>MS without ON (n = 37)</td>
<td>Healthy controls (n = 100)</td>
<td>0.03</td>
</tr>
<tr>
<td>93.19 (±14.41); 63–136</td>
<td>98.44 (±8.81); 79–127</td>
<td></td>
</tr>
<tr>
<td>MS with 1 ON (n = 13)</td>
<td>Healthy controls (n = 100)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>73.85 (±15.20); 50–97</td>
<td>98.44 (±8.81); 79–127</td>
<td></td>
</tr>
<tr>
<td>NMO with 1 ON (n = 26)</td>
<td>NMO without ON (n = 18)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>63.69 (±18.32); 36–94</td>
<td>97.00 (±11.14); 84–116</td>
<td></td>
</tr>
<tr>
<td>MS with 1 ON (n = 13)</td>
<td>MS without ON (n = 37)</td>
<td>0.005</td>
</tr>
<tr>
<td>73.85 (±15.20); 50–97</td>
<td>93.19 (±14.41); 63–136</td>
<td></td>
</tr>
<tr>
<td>NMO with &gt;1 ON (n = 6)</td>
<td>MS with 1 ON (n = 13)</td>
<td>0.03</td>
</tr>
<tr>
<td>50.67 (±8.09); 38–61</td>
<td>73.85 (±15.20); 50–97</td>
<td></td>
</tr>
<tr>
<td>NMO with 1 ON (n = 26)</td>
<td>MS with 1 ON (n = 13)</td>
<td>0.46</td>
</tr>
<tr>
<td>63.69 (±18.32); 36–94</td>
<td>73.85 (±15.20); 50–97</td>
<td></td>
</tr>
<tr>
<td>NMO without ON (n = 18)</td>
<td>MS without ON (n = 37)</td>
<td>0.56</td>
</tr>
<tr>
<td>97.00 (±11.14); 84–116</td>
<td>93.19 (±14.41); 63–136</td>
<td></td>
</tr>
</tbody>
</table>

RNFL values were not associated with EDSS scores ($r = -0.21$, $P = 0.13$, Spearman correlation) but lower RNFL values were associated with longer disease duration ($r = -0.34$, $P = 0.02$, Pearson correlation) when looking at the whole NMO group. No correlation was found when analysis was repeated on the NMO non-ON eyes (EDSS: $r = -0.13$, $P = 0.62$; disease duration: $r = 0.17$, $P = 0.52$) or when analysis was repeated on the NMO ON eyes (EDSS: $r = -0.33$, $P = 0.06$; disease duration: $r = -0.32$, $P = 0.07$).
TABLE 4. Associations between patient characteristics and overall retinal nerve fiber layer thickness using the linear mixed-effects model*

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Overall RNFL Thickness Coefficient (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1 (reference)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>−0.70 (−24.81 to 23.20)</td>
<td>0.95</td>
</tr>
<tr>
<td>Current age (years)</td>
<td>0.02 (−0.59 to 0.64)</td>
<td>0.94</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>−1.68 (−3.19 to −0.16)</td>
<td>0.03</td>
</tr>
<tr>
<td>Disability (EDSS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤≤2</td>
<td>1 (reference)</td>
<td></td>
</tr>
<tr>
<td>≥≥2</td>
<td>1.36 (−19.86 to 22.57)</td>
<td>0.90</td>
</tr>
<tr>
<td>≥≥3 and ≤≤4</td>
<td>−14.92 (−36.93 to 7.10)</td>
<td>0.17</td>
</tr>
<tr>
<td>≥≥5</td>
<td>−7.00 (−29.02 to 15.02)</td>
<td>0.52</td>
</tr>
<tr>
<td>ON</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1 (reference)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>−36.00 (−45.49 to −26.52)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Refraction (diopters)</td>
<td>0.65 (−3.08 to 4.38)</td>
<td>0.72</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1 (reference)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.46 (−15.18 to 18.10)</td>
<td>0.86</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1 (reference)</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>10.11 (−4.82 to 25.03)</td>
<td>0.17</td>
</tr>
<tr>
<td>NMO diagnostic criteria present</td>
<td>1 (reference)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>−12.14 (−27.95 to 3.67)</td>
<td>0.13</td>
</tr>
<tr>
<td>Adjusted models:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disability (EDSS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤≤2</td>
<td>1 (reference)</td>
<td></td>
</tr>
<tr>
<td>≥≥2</td>
<td>0.92 (−16.10 to 17.93)</td>
<td>0.91</td>
</tr>
<tr>
<td>≥≥3 and ≤≤4</td>
<td>0.53 (−17.62 to 18.67)</td>
<td>0.95</td>
</tr>
<tr>
<td>≥≥5</td>
<td>−10.09 (−27.76 to 7.58)</td>
<td>0.25</td>
</tr>
<tr>
<td>ON</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1 (reference)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>−37.06 (−47.07 to −27.06)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>−0.84 (−2.12 to 0.45)</td>
<td>0.19</td>
</tr>
<tr>
<td>ON</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1 (reference)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>−34.78 (−44.38 to −25.17)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*The model accounts for within-patient intereye correlations.
CI, confidence interval; EDSS, expanded disability status scale; NMO, neuromyelitis optica; ON, optic neuritis; RNFL, retinal nerve fiber layer.

**Linear Mixed-Effect Model Analysis**

The linear mixed-effects model indicated that the mean RNFL measurements were not associated with gender, age, disability (EDSS), refraction, IMD, ethnicity, or NMO diagnostic criteria status (P > 0.1, Table 4), although RNFL measurements were associated with a history of ON (P < 0.001, Table 4) and disease duration (P = 0.03). If the model was adjusted for history of ON, neither EDSS nor disease duration was associated with RNFL thickness (P > 0.1).

**DISCUSSION**

Histopathologically, NMO is characterized by acute inflammation associated with neutrophilic and eosinophilic infiltrate, demyelination, and destructive necrotizing cavitation, with vascular hyalinization (thickening) and IgG and complement deposition, which destroys perivascular neural parenchyma (15,16). The intense inflammatory activity in NMO eyes can result in pronounced RNFL atrophy. However, MS lesions exhibit demyelination and inflammation with less axonal loss than in NMO (8), indicating the potential to distinguish NMO from MS, based on severity of RNFL loss after an episode of ON.

Our primary objective was to compare RNFL thickness between NMO, RRMS patients, and healthy controls and to evaluate if severity of RNFL deficit could help distinguish NMO patients early in their disease. We observed RNFL thinning in NMO ON eyes compared with unaffected eyes or healthy control eyes, whereas unaffected NMO eyes were not significantly different from healthy controls.
Ratchford et al (8) reported, in a cross-sectional study on 26 NMO patients, a small difference in RNFL between NMO non-ON eyes (n = 8) and healthy controls (97.9 m in NMO, 96.3 m in TM, and 102.4 m in healthy controls), all of which were not significantly different (Table 5). We used the newer generation SD-OCT with higher resolution and a larger sample size (n=18) and did not find any significant difference between these groups. This may be due to the more acute course of NMO relapses with no significant disease activity between such episodes (i.e., secondary progressive pattern) (17) compared with gradual RNFL loss observed in MS (18) patients mainly due to on-going brain atrophy that implicates a different pathophysiology.

Naismith et al (15) and Nakamura et al (19) have shown more severe RNFL thinning inferiorly and superiorly in NMO eyes compared with MS eyes. In our study, this was not the case. One reason could be that we used the higher resolution SD-OCT compared with the Stratus OCT, which is harder to center and only slight decentration can result in artificial thinning. Other authors also have shown similar differences in RNFL thickness between MS ON eyes and NMO ON eyes (16) and MS ON eyes, NMO eyes, and healthy controls (20,21) using older time domain-OCT technology (Table 5).

Due to a relatively large overlap between RNFL value ranges in NMO eyes with a single episode of ON and MS eyes with ON, it is difficult to use RNFL to differentiate between NMO and MS ON (Table 2). In contrast to MS ON eyes, we found no difference between the unaffected NMO eyes and the healthy controls. Therefore, an alternative might be to use the intereye difference in RNFL values between affected and unaffected eyes in patients with a history of an isolated ON event to distinguish NMO from MS ON. Our data showed a difference of 36.3 mm (n = 10) in the NMO group compared with 16.7 mm (n = 3) in the MS group. Unfortunately, the majority of the MS cohort studied consisted of patients with bilateral sequential ON, and only 3 patients with unilateral ON in the MS group. We found that a difference of more than 20 μm in RNFL was more likely to occur in NMO (70%, 7 of 10) than in MS (33%, 1 of 3) eyes. This could be a better diagnostic marker than RNFL in ON eyes alone because it uses both findings.

### Table 5. Published reports of RNFL thickness in patients with NMO and MS

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Number of eyes</th>
<th>Gender F/M</th>
<th>Mean age</th>
<th>Mean EDSS</th>
<th>Mean RFNL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratchford et al (8)</td>
<td>26</td>
<td>22</td>
<td>17/5</td>
<td>41 (13)</td>
<td>4.5</td>
<td>63.6 (20.3)</td>
</tr>
<tr>
<td>Naismith et al (15)</td>
<td>22</td>
<td>30</td>
<td>14/1</td>
<td>42.9</td>
<td>5.2</td>
<td>54.8 (3.7)</td>
</tr>
<tr>
<td>De Seze et al (20)</td>
<td>35</td>
<td>62</td>
<td>20/9</td>
<td>40.6</td>
<td>5.2</td>
<td>74.2</td>
</tr>
<tr>
<td>Merle et al (21)</td>
<td>15</td>
<td>25</td>
<td>14/1</td>
<td>41</td>
<td>3.5</td>
<td>65.44</td>
</tr>
<tr>
<td>Green and Cree (16)</td>
<td>16</td>
<td>24</td>
<td>16/2</td>
<td>41</td>
<td>3.5</td>
<td>59.2</td>
</tr>
<tr>
<td>Nakamura et al (19)</td>
<td>36</td>
<td>46</td>
<td>18/0</td>
<td>46.6</td>
<td>4.9</td>
<td>63.8</td>
</tr>
<tr>
<td>Current Study</td>
<td>31</td>
<td>30</td>
<td>17/12</td>
<td>50.1</td>
<td>3.4</td>
<td>63.9</td>
</tr>
</tbody>
</table>

EDSS, expanded disability status scale; F, female; M, male; MS, multiple sclerosis; NMO, neuromyelitis optica; NON, no optic neuritis; OCT, optical coherence tomography; ON, optic neuritis; RNFL, retinal nerve fiber layer.
and integrates them in a single number. This was also suggested by Ratchford et al (8), noting that after a first episode of unilateral ON, RNFL difference of more than 15 μm between eyes should prompt consideration of an NMO spectrum disorder. Distinguishing NMO from MS based on the difference in RNFL thickness after unilateral ON requires further studies comparing larger cohorts of NMO and MS patients with a history of unilateral ON to establish a reliable threshold to separate the 2 entities.

Shortcomings of our study primarily were due to a relatively small sample size and type of patients enrolled. As we were trying to find a diagnostic test that helps identifying NMO patients early in the disease stage, diagnosis of NMO spectrum disorders was based on clinical diagnosis of the neurologist (reviewed by 2 other independent neurologists) rather than on seropositivity. This might explain our small number of seropositive patients in the NMO group.

Our data showed that RNFL in NMO ON eyes is significantly reduced compared with the unaffected eyes or eyes of healthy controls, but the unaffected eyes were not significantly different from healthy control eyes. RNFL in NMO is not different enough to distinguish NMO ON from MS ON eyes, but a value of more than 20 μm difference in RFNL between eyes should prompt consideration of an NMO diagnosis of unilateral ON, RNFL difference of more than 15 μm between eyes is a relatively small sample size and type of patients enrolled.

REFERENCES

The Retinal Nerve Fiber Layer of Patients With Neuromyelitis Optica and Chronic Relapsing Optic Neuritis is More Severely Damaged than Patients With Multiple Sclerosis

Denis B. Bichuetti, MD, PhD, André S. de Camargo, MD, Alessandra B. Falcão, MD, Fabiana F. Gonçalves, MD, Ivan M. Tavares, MD, PhD, Enedina M.L. de Oliveira, MD, PhD

Background: To compare the retinal nerve fiber layer (RNFL) in eyes of patients with relapsing remitting multiple sclerosis (RRMS), neuromyelitis optica (NMO) and chronic relapsing inflammatory optic neuritis (CRION).

Methods: Evaluation of 62 patients with RRMS, NMO, and CRION in a cross-sectional study with spectral domain optical coherence tomography.

Results: A total of 124 eyes were evaluated (96 RRMS, 18 NMO, and 10 CRION). Frequency of optic neuritis for each disease was: 34% for RRMS, 84% for NMO, and 100% for CRION. Visual acuity and RNFL thickness were significantly worse in NMO and CRION eyes than in RRMS, but there were no differences between NMO and CRION eyes. A RNFL of 41 μm was 100% specific for optic neuritis associated with NMO and CRION when compared to RRMS.

Conclusion: This study established RNFL values to differentiate optic neuritis of RRMS from NMO and CRION. Although similarities observed between NMO and CRION eyes might suggest that they are within the same disease spectrum, it is still recommended that these 2 conditions be differentiated on clinical grounds. Optical coherence tomography serves as an additional diagnostic tool and can be used to monitor disease progression.


The differential diagnosis of optic neuritis (ON) continues to expand. The clinician must not only differentiate ON associated with multiple sclerosis, (1) infectious causes, and autoimmune conditions (2,3) but must also include neuromyelitis optica (NMO) (4) and cases of recurrent ON without clinical evidence of disease beyond the anterior visual pathways (5–10). The discovery of aquaporin-4 antibody (NMO-IgG) (11) has shown that many inflammatory diseases of the central nervous system, including recurrent longitudinally extensive transverse myelitis, recurrent ON, and recurrent brainstem and encephalic syndromes, may fall within the disease spectrum of aquaporin-4 autoimmunity called NMO spectrum disorders (NMO-SD) (12,13).

In their original report of chronic relapsing inflammatory optic neuritis (CRION), Kidd et al (5) described patients with bilateral inflammatory optic neuritis with recurrent relapses over time and that worsened upon steroid or immunosuppression withdrawal. This led to reports differentiating other forms of relapsing ON from CRION (6–8). It is unclear whether there is a chronic progressive or relapsing course in CRION patients, because these patients tend to relapse upon medication withdrawal in weeks to months.
Possibly, some patients with CRION would fit into NMO-SD (14,15).

Optical coherence tomography (OCT) has been used to evaluate RNFL thickness in various diseases, including multiple sclerosis, neuromyelitis optica, and clinical isolated syndromes (16–19). We performed a single center cross-sectional study comparing the visual acuity and RNFL thickness with spectral domain optical coherence tomography (SD-OCT) in patients with relapsing remitting multiple sclerosis (RRMS), NMO, and CRION, to assess whether this technique could distinguish ON in these 3 disorders.

METHODS

We recruited patients with RRMS, NMO, and CRION seen in 2010 and 2011 in the neuroimmunology clinic at the Federal University of São Paulo, São Paulo, Brazil. Patients had to satisfy diagnostic criteria for RRMS (20) and NMO (21), while those with CRION experienced at least 2 inflammatory ON episodes 30 days apart without clinical or radiological signs of disease activity elsewhere in the central nervous system. We classified the patients with CRION if they had suffered >1 relapse of ON in the same, fellow, or both eyes, regardless of whether they were previously immunosuppressed. All patients had at least 1 brain and spinal cord magnetic resonance imaging (MRI) study at the first evaluation and were screened for autoimmune and systemic causes. This included testing for human immunodeficiency virus, hepatitis B and C, human T-cell lymphotropic virus, syphilis, toxoplasmosis, and cytomegalovirus. A thorough review of systems was completed on CRION patients to exclude a potential toxic or genetic cause.

Patients had an expanded disability status scale (EDSS) score of 0–5.5. Peripapillary RNFL thickness was measured by SD-OCT, using the Spectralis software (version 4.0, Heidelberg Engineering, Dossenheim, Germany). Only well-focused, evenly illuminated, and centered images were included in the analysis.

We collected demographic, clinical, laboratory, and MRI data of all patients. NMO-IgG testing using indirect immunofluorescence was performed in all patients with NMO or CRION seen after 2007, as this test was not available in Brazil before that date. Thus, some samples came from patients already on immunosuppressive medication, which is known to reduce the sensitivity of the test (22,23). To avoid bias because of disease duration, we normalized the EDSS (24) on last follow-up visit and total number of relapses by the total time of disease (in years), thus using the progression index (PI) and annualized relapse rate (25). Because patients with CRION would have a maximum EDSS of 4 due to conversion of visual functional system scores on the final EDSS step, we categorized each patient’s visual acuity (VA) in each eye according to the EDSS visual functional system score (0 = normal; 1 = VA 20/20 to 20/29; 2 = VA 20/30 to 20/59; 3 = VA 20/60 to 20/99; 4 = VA 100 to 20/199; and 5 = VA worse than 20/200) and calculated the PI exclusively for this system. Almost all patients received treatment with 1 or a combination of drugs including corticosteroids, azathioprine, methotrexate, cyclophosphamide, interferon beta, glatiramer acetate, natalizumab, and IV immunoglobulin.

Statistical analysis was performed using GraphPad Prism version 5.0f, with data presented as mean ± SD or median and interquartile range. Unpaired t test was used when comparing 2 groups, and analysis of variance was used when appropriate. A receiver–operator characteristic curve (ROC curve) was established to estimate sensitivity and sensitivity to differentiate these diseases through the use of OCT. The Internal Review Board of the Universidade Federal de São Paulo approved our study, and written informed consent was obtained from all subjects before the performance of the neuroophthalmologic and SD-OCT examinations.

RESULTS

Sixty-two patients completed neuroophthalmologic and SD-OCT examinations: 48 with RRMS, 9 with NMO, and 5 with CRION. OCT and EDSS results in patients with optic neuritis are shown in Table 1.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Age of Onset Duration, y</th>
<th>History of Optic Neuritis (Eyes)</th>
<th>Age OCT Was Performed</th>
<th>RNFL, μm</th>
<th>EDSS Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRMS, n = 48</td>
<td>29.9 (±10.4)</td>
<td>8.7 (±5.9)</td>
<td>33 (34%)</td>
<td>38.6 (±11.8)</td>
<td>87.7 (±15.3)</td>
</tr>
<tr>
<td>NMO, n = 9</td>
<td>30.3 (±9.3)</td>
<td>8.6 (±3.2)</td>
<td>15 (±84%)</td>
<td>39.0 (±10.5)</td>
<td>65.8 (±20.9)</td>
</tr>
<tr>
<td>CRION, n = 5</td>
<td>36.2 (±6.7)</td>
<td>7.0 (±8.9)</td>
<td>10 (100%)</td>
<td>43.0 (±6.3)</td>
<td>48.9 (±15.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease</th>
<th>Visual</th>
<th>Pyramidal</th>
<th>Cerebellar</th>
<th>Sensory</th>
<th>Brainstem</th>
<th>PI</th>
<th>PI Visual</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRMS, n = 48</td>
<td>1.2 (±1.5)</td>
<td>1.3 (±1.1)</td>
<td>0.4 (±0.9)</td>
<td>0.7 (±0.9)</td>
<td>0.1 (±0.3)</td>
<td>0.3 (±0.2)</td>
<td>0.2 (±0.3)</td>
</tr>
<tr>
<td>NMO, n = 9</td>
<td>3.5 (±1.8)</td>
<td>1.1 (±0.6)</td>
<td>0.0 (±0.0)</td>
<td>0.7 (±1.0)</td>
<td>0.0 (±0.0)</td>
<td>0.4 (±0.2)</td>
<td>0.4 (±0.3)</td>
</tr>
<tr>
<td>CRION, n = 5</td>
<td>4.2 (±1.2)</td>
<td>0.0 (±0.0)</td>
<td>0.0 (±0.0)</td>
<td>0.0 (±0.0)</td>
<td>1.0 (±0.6)</td>
<td>1.1 (±0.7)</td>
<td></td>
</tr>
</tbody>
</table>

Parentheses denote standard deviation.

CRION, chronic relapsing inflammatory optic neuritis; EDSS, expanded disability status score; FS, functional system; NMO, neuromyelitis optica; OCT, optical coherence tomography; PI, progression index; RNFL, retinal nerve fiber layer; RRMS, relapsing remitting multiple sclerosis.
(8 relapsing and 1 monophasic), and 5 with CRION. Of the 124 eyes evaluated with SD-OCT, only 99 were of sufficient quality for interpretation (79 from RRMS, 12 from NMO, and 8 from CRION) (See Supplemental Digital Content, Table 1, http://links.lww.com/WNO/A80). The main reasons for inadequate quality were nystagmus and difficulty in maintaining steady fixation because of impaired VA. Thirty-four percent of eyes from patients with RRMS, 84% of the eyes from patients with NMO, and all eyes from patients with CRION experienced at least 1 episode of ON. Age of onset and age at SD-OCT measurements did not differ between the groups (ANOVA with Bonferroni multiple comparison test) and disease duration was also similar (ANOVA with Dunn multiples comparison test) (Table 1). Last measured VA was worse in NMO and CRION eyes than RRMS ($P < 0.0001$ for NMO or CRION vs RRMS and $P = 0.4703$ for NMO vs CRION), but there was no difference between NMO and CRION ($P = 0.4703$). The PI for visual functional system of patients with NMO was worse than patients with RRMS ($P < 0.0001$), and patients with CRION had higher rates than patients with NMO ($P < 0.0075$). Clinical comparison of other aspects of the expanded EDSS was not possible, as patients with NMO and CRION presented with fewer neurologic symptoms, and the analysis would be biased towards worse results in RRMS patients. Since only patients with mild-to-moderate EDSS were recruited, patients with RRMS presented low scores on other functional systems as well.

NMO-IgG testing was performed in all patients categorized as NMO or CRION, with 45% and 20% positivity, respectively. Patients who fulfilled criteria for multiple sclerosis were not routinely tested for NMO-IgG, because this test has limited value in the typical multiple sclerosis patient (26). However, 7 patients with RRMS were tested for NMO-IgG, all with negative results.

In evaluating eyes with ON, patients with RRMS had RNFL substantially thicker than patients with NMO or CRION (Table 2). There was no statistical difference in the RNFL between NMO and CRION eyes. We analyzed eyes by the number of ON episodes (0, 1, 2, and $\geq 3$) to identify whether the differences observed in RNFL were an effect of the number of relapses or severity (Tables 3 and 4). This appeared to have no effect, that is, NMO and CRION eyes were more severely affected than RRMS, but without a significant difference between them (Table 4). Although the number of eyes was small, there was no difference in RNFL thickness and VA between the 63 eyes from RRMS patients and the 3 eyes from NMO patients who lacked a history of ON.

An ROC curve was created comparing eyes that had ON from patients with RRMS, NMO, and CRION to establish sensitivity and specificity values that could differentiate these conditions. The eyes from RRMS patients were used as controls and the eyes from NMO and NMO + CRION were pooled together (Fig. 1). The comparison of RRMS eyes to NMO with an ROC curve presented an area under the curve (AUC) of 0.7991 with $P = 0.0083$, and when using NMO and CRION eyes pooled together as patients and RRMS as controls, an AUC of 0.8507 with $P = 0.0001$. In both cases, a RNFL thickness of 41 μm or less was 100% specific for ON associated with NMO or CRION when compared to RRMS. None of the eyes from RRMS patients had values below 41 μm, as opposed to 2 with NMO (1 patient) and 4 with CRION (3 patients).

**DISCUSSION**

The recognition of distinct clinical and pathophysiological features of NMO-SD has placed these conditions into

### TABLE 2. Retinal nerve fiber layer thickness comparisons in eyes with optic neuritis

<table>
<thead>
<tr>
<th></th>
<th>RRMS vs NMO</th>
<th>RRMS vs CRION</th>
<th>NMO vs CRION</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P$</td>
<td>0.0040</td>
<td>$&lt;0.0001$</td>
<td>0.2149</td>
</tr>
</tbody>
</table>

Unpaired t test was used in analysis.

CRION, chronic relapsing inflammatory optic neuritis; NMO, neuromyelitis optica; RRMS, relapsing remitting multiple sclerosis.

**TABLE 3. Comparison of EDSS scores and RNFL thickness in patients with RRMS, NMO, and CRION based on the number of episodes of optic neuritis**

<table>
<thead>
<tr>
<th>Episodes</th>
<th>RRMS</th>
<th>NMO</th>
<th>CRION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Visual FS</td>
<td>RNFL</td>
</tr>
<tr>
<td>0</td>
<td>63</td>
<td>0.0 (0.0–1.5)</td>
<td>92.4 (±14.0)</td>
</tr>
<tr>
<td>1</td>
<td>26</td>
<td>2.0 (0.75–4.3)</td>
<td>80.1 (±14.8)</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>2.0 (1.3–2.0)</td>
<td>61.7 (±7.1)</td>
</tr>
<tr>
<td>$\geq 3$</td>
<td>3</td>
<td>1.0 (0.0–3.0)</td>
<td>81.3 (±17.5)</td>
</tr>
</tbody>
</table>

Data is represented as median and 25th and 75th percentiles in parenthesis.

*No eye in this category.
†Single eye.

CRION, chronic relapsing inflammatory optic neuritis; EDSS, expanded disability status score; FS, functional system; NMO, neuromyelitis optica; RNFL, retinal nerve fiber layer; RRMS, relapsing remitting multiple sclerosis.
TABLE 4. Statistical analysis of EDSS visual system function score and RNFL thickness in patients with RRMS, NMO, and CRION based on the number of episodes of optic neuritis

<table>
<thead>
<tr>
<th>Category</th>
<th>RRMS vs NMO</th>
<th>RRMS vs CRION</th>
<th>NMO vs CRION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual FS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Episodes of ON</td>
<td>0</td>
<td>0.6501</td>
<td>*</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0.0671</td>
<td>0.0259</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.0042</td>
<td>0.0036</td>
</tr>
<tr>
<td></td>
<td>≥3</td>
<td>τ</td>
<td>0.1161</td>
</tr>
<tr>
<td>RNFL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Episodes of ON</td>
<td>0</td>
<td>0.4355</td>
<td>*</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0.0532</td>
<td>0.0008</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.0531</td>
<td>0.0198</td>
</tr>
<tr>
<td></td>
<td>≥3</td>
<td>τ</td>
<td>τ</td>
</tr>
</tbody>
</table>

Unpaired t test was used in all analysis.
*No eye with CRION in this category.
†No eye with NMO in this category.
‡Comparison not possible as there is only 1 eye with CRION with adequate quality optical coherence tomography in this category.
CRION, chronic relapsing inflammatory optic neuritis; EDSS, expanded disability status score; FS, functional system EDDS score; NMO, neuromyelitis optica; ON, optic neuritis; RNFL, retinal nerve fiber layer; RRMS, relapsing remitting multiple sclerosis.

A separate category of CNS inflammatory disorders (12,27,28). In this context, we demonstrated that changes in RNFL thickness of optic neuritis patients with CRION are similar to NMO, and both are distinct from RRMS.

Previous reports of relapsing ON not related to RRMS have included patients with severe visual loss and a mean age of onset between 20 and 50 years. Nearly 50% of relapses occur within 1 year, but in some up to 10 years (5–8, 29, 30). The rate of NMO-IgG positivity in relapsing ON has been reported between 20% and 50% (7, 8, 10, 29, 30), and with nearly 50% of patients with relapsing ON converting to NMO (29,31).

We recognize the limitations of our study. All patients with RRMS received immunomodulatory treatment, and all patients with NMO and all but 1 with CRION were given immunosuppressive medication. This likely biased our analysis due to treatment duration and intensity. Patients exclusively with ON relapses were less likely to receive treatment or receive it later in the clinical course than those with additional neurologic findings (data not shown). This delay could have contributed to differences in RNFL thickness between NMO and CRION. Also, the selection of RRMS and NMO patients with low-to-moderate EDSS scores created a cohort bias. Yet, this allowed us to include patients within the first 10 years of disease onset, producing a more homogenous sample of patients with similar disease duration. Although statistical comparison of RNFL thickness from patients with RRMS and NMO with 1 or 2 ON episodes was not significant (Table 4), differing from the analysis of all eyes together (Table 2), we believe that this trend was due to splitting the groups into smaller samples and reducing statistical power. The inclusion of patients after their first clinical event, as performed by Collongues et al (32), requires a longitudinal study, which is currently underway in our center.

Our study has shown that in patients with ON, measurement of RNFL thickness is similar in NMO and CRION patients compared to those with RRMS. Although the value of 41 μm for RNFL thickness is 100% specific for NMO and CRION, and may assist in differentiation from...
RRMS, establishing the diagnosis of these 3 disorders still rests on clinical, neuroimaging, and serologic findings.

REFERENCES


Maculopathy and Spinocerebellar Ataxia Type 1: A New Association?

Pierre Lebranchu, MD, Guylène Le Meur, MD, PhD, Armelle Magot, MD, Albert David, MD, Christophe Verny, MD, PhD, Michel Weber, MD, PhD, Dan Milea, MD, PhD

Background: Autosomal dominant cerebellar ataxia is a rare heterogeneous group of diseases characterized by cerebellar symptoms, often associated with other multisystemic signs. Mild optic neuropathy has been associated with spinocerebellar ataxia type 1 (SCA1), but macular dysfunction has been reported in only 2 cases. We report the first family with SCA1 with several members affected by visual loss related to maculopathy.

Methods: Cross-sectional clinical and electrophysiological study of a family with genetically confirmed SCA1. Patients with unexplained visual loss were included.

Results: Four patients from the same family, carrying the same genetic mutation, were examined. Testing revealed an increased CAG trinucleotide repeat number within the SCA1 gene. Genetic testing results for SCA7 were negative. Visual acuities ranged between 20/20 and 20/200. Visual fields revealed central scotomas in most of the eyes, and funduscopy was unremarkable in most patients. Central retinal thinning of the retina or disorganized photoreceptor layers were found with optical coherence tomography (OCT). In one patient, multifocal electroretinography (mfERG) revealed central retinal dysfunction.

Conclusions: A clinically subtle or even occult maculopathy can occur in association with SCA1. Macular OCT and mfERG can be abnormal even in asymptomatic patients. Unexplained visual loss in SCA1 patients should prompt evaluation of macular function, even if clinical signs of maculopathy are absent.

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Autosomal dominant cerebellar ataxia (ADCA) is a rare heterogeneous group of diseases characterized by cerebellar symptoms, often associated with other neurological signs. To date, 20 associated genes have been identified, with the phenotypic spectrum ranging from isolated ataxia to multisystemic deficits. Overall, prevalence ranges from 2 to 7 per 100,000 people (1).

Spinocerebellar ataxia type 1 (SCA1) usually is diagnosed in the 4th decade, with the most common neurologic signs being limb ataxia and dysarthria. Ophthalmological signs may initially include nystagmus and saccadic hypometria, eventually associated with ophthalmoparesis or mild optic neuropathy as the disease progresses. In SCA7, macular dystrophy can be associated with ataxia (2).

All SCA1 (3) and most of SCA7 mutations correspond to a CAG trinucleotide expansion within the gene’s coding region (<2-cm segment on 6p23 chromosome for SCA1 and 3p21.1-p12 for SCA7). Less often, SCA7 patients exhibit a large deletion within the gene. Both SCA1 and SCA7 mutations are usually caused by polyglutamine expansion, manifesting above a threshold of CAG repeats. There is a strong association between the clinical severity of the disease, the age of first symptoms, and the number of CAG repeats (4). Anticipation, which explains the younger age of onset of symptoms in successive intrafamilial generations, results from CAG repeat expansion upon transmission.

SCA7 has a specific association with retinal pathology. This degenerative retinopathy initially affects cones, before progressing to cone–rod dystrophy (2). Fundus examination
demonstrates macular pigmentary changes, sometimes associated with mild temporal optic disc pallor (5). The gene encodes for a protein (ataxin-7), widely expressed in human retina but of unknown function (6). This protein may interact with the function of CRX (cone–rod homeobox), a known transcription factor implicated in human cone–rod dystrophy (7).

Other maculopathies associated with SCAs are very rare. To our knowledge, only 2 single case reports (8,9) have been previously described a maculopathy in SCA1. In both cases, the retinal changes were caused by a late onset of clinically detectable pigmentary macular dystrophy, associated with abnormal electroretinography (ERG), revealing rod and cone dysfunction. The aim of this study was to report the first family with genetically identified SCA1 associated with a maculopathy.

METHODS

Four patients from the same family (Fig. 1) were included in the study. All had a complete ophthalmological examination and automated static perimetry, fundus photography, and optical coherence tomography (OCT). Patient 1 underwent additional testing, including microperimetry, visual evoked potentials (VEP), full-field ERG, and multifocal electroretinography (mfERG). Details of previous genetic and neurological examinations were extracted from medical charts with patient’s permission. After informed consent, DNA from family members was analyzed for SCA1 and SCA7 gene mutations (Table 1).

RESULTS

Patient 1
A 51-year-old man reported a 6-month history of bilateral, progressive painless visual loss. His medical history included surgical removal of a pituitary adenoma 9 years earlier with full recovery of visual fields. One year before vision loss, the patient was evaluated for mild ataxia and swallowing difficulties. Diagnosis of SCA1 was confirmed via molecular analysis with a 42 CAG repeat expansion in one allele. Visual acuity was 20/32, right eye, and 20/40, left eye. Lanthony desaturated 15-hue color testing was abnormal, with a green–red axis on the right side and without axis on the other side. Visual field testing disclosed bilateral central scotomas (Fig. 2). On funduscopy, there were small drusen around the fovea and mild temporal optic disc pallor (Fig. 3). Retinal autofluorescence revealed central pigment irregularities in both eyes. OCT disclosed disorganization of the macular photoreceptor layer bilaterally (Fig. 4) and thinning of the temporal retinal nerve fiber layer (RNFL) (Table 2). Microperimetry revealed a decrease of retinal sensitivity (threshold ranging from 0 to 8 dB) in the 2-mm central area, with a relative sparing of the perifoveal surrounding area (threshold ranging from 8 dB to 10 dB). Comparison between function and anatomy confirmed the decrease of sensitivity in the area where the photoreceptor layer was laminated (Fig. 5). Full-field ERG was normal but mfERG confirmed macular dysfunction in each eye. VEP disclosed mildly increased P100 latencies and decreased P100 amplitudes.

Patient 2
A 73-year-old woman had a long history of ataxia and unexplained visual loss. She had suffered a slow deterioration in her ability to walk since her 50s and dysarthria since her 60s. No cognitive disabilities were reported. Visual acuity was 20/50, right eye, and 20/80, left eye. Visual field results were not reliable. Macular drusen were present bilaterally (Fig. 3), and retinal autofluorescence was suggestive of central atrophy. The optic discs were normal. Fluorescein angiography showed mild granular appearance of the perifoveal retinal pigmentary epithelium (RPE). Macular OCT revealed bilateral macular atrophy with an abnormal foveal lamination pattern between the external layers. Focal thickening of the retinal pigment epithelium complex was present in the right eye (Fig. 4). Measurement of macular and global RNFL thickness was normal (Table 2).

Patient 3
A 55-year-old woman, with severe ataxia that began 13 years earlier complained of bilateral, progressive painless visual loss. Serial neurological examinations revealed slowly

FIG. 1. Genealogical tree of the family. Square = male, circle = female, black = SCA1 patients.
progressive kinetic and static cerebellar syndrome, associated with tetrapyramidal signs and speech and swallowing difficulties. Marked ponto-cerebellar atrophy was detected on magnetic resonance imaging (MRI). Visual acuity was 20/200, right eye, and 20/100, left eye. Visual fields showed bilateral central scotomas. Funduscopy revealed only mild granular appearance of the foveal RPE (Fig. 3). There was RNFL thinning on OCT (Table 2) and abnormal foveal cavitation was visible, between the outer segment layer and the layer representing the junction of the inner and outer segments. The layer corresponding to the retinal epithelium complex exhibited local foveal thickening (Fig. 4).

Patient 4
A 52-year-old man, with no visual complaints, had a history of slowly progressive cerebellar–pyramidal syndrome. MRI showed marked cerebellar atrophy, and genetic analysis confirmed SCA1 diagnosis. Other causes of genetic spinocerebellar ataxia were excluded (SCA 2, 3, 6, 7, 12, and 17). Visual acuity was 20/20 bilaterally. Macular visual field testing revealed asymptomatic, asymmetric central scotomas. Funduscopy was normal (Fig. 3), but OCT revealed central alteration of the photoreceptor outer segment layer, with focal thickening (Fig. 4). RNFL thickness was normal (Table 2).

DISCUSSION
Optic neuropathy has been reported previously as a cause of visual impairment in SCA1. Abe et al (10) reported 6 SCA1 patients from 3 families with decreased visual acuity and optic atrophy. Using OCT, Stricker et al (11) demonstrated significant thinning of temporal retinal nerve fibers, suggesting preferential involvement of the papillomacular bundle. Abnormalities of both latency and amplitude of VEPs also have been found in SCA1 patients (12–14). In most of these studies, the retinal function was tested using full-field ERG; mfERG was not performed.

Among ADCA, SCA7 has been associated with retinal disease (15), ranging from minor retinal findings (slightly attenuated retinal arteries, mild temporal disc pallor, normal fundus autofluorescence (16)) to severe visual loss (17). Macular OCT in SCA7 patients has confirmed both quantitative macular thinning and qualitative altered foveal lamination of the photoreceptor layer at early stages of disease (18,19). There is an increasing evidence of macular abnormalities occurring in ADCA patients, being 2.7 times more common in ataxic patients (20). Stricker et al (11) found decreased total macular volume with OCT in 6 SCA1 patients, but this was not statistically significant. Using OCT, Pula et al (21) found a significant thinning of macular volume at 3 mm in 7 SCA1 patients, and Vaclavik et al (22) described a SCA1 patient with maculopathy and retinal dysfunction. Thurtell et al (9) reported a case of a genetically proven SCA1 patient with visual loss also secondary to rod–cone dystrophy, whose clinical findings were very similar to those of our patients: bilateral, progressive painless visual loss with macular drusen and mild pigmentary alterations on fundus examination. Other members of this reported

---

**TABLE 1.** Demographic and genetic data of SCA1 patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, yr</th>
<th>Gender</th>
<th>Number of CAG Repeats</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>51</td>
<td>Male</td>
<td>42–30</td>
</tr>
<tr>
<td>P2</td>
<td>73</td>
<td>Female</td>
<td>41–28</td>
</tr>
<tr>
<td>P3</td>
<td>55</td>
<td>Female</td>
<td>41–28</td>
</tr>
<tr>
<td>P4</td>
<td>52</td>
<td>Male</td>
<td>44–28</td>
</tr>
</tbody>
</table>

SCA1 gene given for both alleles.

*Because of typical neurological findings, no genetic analysis was performed on patient 3 (sister of P4).
family (9) exhibiting the SCA1 mutation also complained of visual loss, but no details of their fundus examination were reported.

We can only speculate why several related patients exhibiting the same SCA1 mutation were affected by a maculopathy, with heterogeneous intrafamilial expression. A common finding in SCA1 patients is phenotypic variability because of the number of CAG repeats among affected patients (23). To explain the occurrence of both neurological and ophthalmological diseases in this family, the hypothesis of 2 independently segregated traits cannot be excluded, but the evidence is weak. The probability of an

**FIG. 3.** Fundus appearance of SCA1 patients (P1, P2, and P3) shows mild granular appearance of the perifoveal retinal pigment epithelium and small drusen around the foveola. Funduscopy was normal in P4.

**FIG. 4.** OCT in patients with SCA1 (P1, P2, P3, and P4) reveals altered foveal lamination and abnormal space between the retinal pigment epithelium and external limiting membrane.
SCA1 family exhibiting an hereditary macular disease is equal to that of the general population, less than 1/40,000 (24). The probability of 4 relatives harboring 2 separate autosomal dominant diseases is even lower. It is more likely that both diseases are genetically linked, either with 2 independent mutations nearby on the same chromosome or because of a “local effect” of one mutation on another gene nearby.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Side</th>
<th>Visual acuity</th>
<th>Macular (μm)</th>
<th>Average RNFL (μm)</th>
<th>Temporal RNFL (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>R</td>
<td>20/32</td>
<td>220 (H) 174 (N)</td>
<td>71 (H)</td>
<td>34 (H)</td>
</tr>
<tr>
<td>L</td>
<td>20/40</td>
<td>226 (H) 183 (N)</td>
<td>77 (H)</td>
<td>43 (H)</td>
<td></td>
</tr>
<tr>
<td>P2</td>
<td>R</td>
<td>20/50</td>
<td>181 (C)</td>
<td>97 (C)</td>
<td>NA</td>
</tr>
<tr>
<td>L</td>
<td>20/80</td>
<td>188 (C)</td>
<td>97 (C)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>P3</td>
<td>R</td>
<td>20/200</td>
<td>173 (C)</td>
<td>96 (C)</td>
<td>59 (C)</td>
</tr>
<tr>
<td>L</td>
<td>20/100</td>
<td>156 (C)</td>
<td>94 (C)</td>
<td>58 (C)</td>
<td></td>
</tr>
<tr>
<td>P4</td>
<td>R</td>
<td>20/20</td>
<td>189 (C)</td>
<td>90 (C)</td>
<td>61 (C)</td>
</tr>
<tr>
<td>L</td>
<td>20/20</td>
<td>187 (C)</td>
<td>99 (C)</td>
<td>64 (C)</td>
<td></td>
</tr>
</tbody>
</table>

Measurement done with spectral-domain optical coherence tomography Heidelberg (H), Nidek MP1 microperimeter (N), and Cirrus HD-OCT (C).


L, left; NA, not available; R, right; RNFL, retinal nerve fiber layer.

FIG. 5. Microperimetry recordings in P1. Right (A) and left (B) macular sensitivity, tested in 29 different points. The number above each point represents the sensitivity (in decibels) found in each portion of the retina. Color scale: green = sensitivity threshold found in 95% of the population; yellow = deficit of sensitivity found in less than 5% of the population; red = deficit of sensitivity found in less than 1% of the population. Right (C) and left (D) macular thickness. Macula is divided in 9 regions, and the average thickness (in micrometer) of each is indicated numerically. Color scale: green = thickness observed in 95% of a normal population; yellow = abnormal thickness observed in less than 5%; and red = abnormal thickness observed in less than 1%.
Pathogenesis of SCA1 is due partly to direct mutation of the gene (6p22.3), translated into an abnormal protein (ataxin-1) that has an abnormally long stretch of glutamine. This leads to polyQ protein aggregation in the cell and aberrant protein interactions, with specific transcriptional complexes in the nucleus (25). Trinucleotide repeat disorder could exhibit other pathogenic manifestations, secondary to direct accumulation of the mutant messenger RNA in the nucleus, indirect gain of function (26), or inhibition of adjacent gene (27). In our patients, OCT demonstrated alterations of the external layers of the fovea, suggesting a loss of the structural integrity of the photoreceptors. Clinically, this foveolar laminar is compatible with an adult-onset vitelliform maculopathy, but the thinning of the whole macular area (including the surrounding perifoveolar retina) could be related to a cone dystrophy. Cone dystrophy is a clinically and genetically heterogeneous group, and no standard screening test has been developed. More than 10 different genes and loci have been identified in autosomal dominant cone dystrophy (https://sph.uth.edu/Retnet/sum-dis.htm#A-genes). Interestingly, a cluster of genes (GUCA1A, PRPH2) implicated in a spectrum of macular disease is located in 6p21.1, nearby SCA1 mutation. The gene GUCA1A (guanylate cyclase activator 1A) is implicated in cone dystrophy (COD3), which has phenotypic variability, even in the same family (28,29). The gene PRPH2 (Peripherin 2) has also been identified in adult-onset vitelliform macular dystrophy (30) or adult-onset foveomacular dystrophy (31). On inhibiting one of its promoters, CAG trinucleotide repeat could interfere with the regulation of one of these genes.

Establishing a definite association of a maculopathy with SCA1 is limited, in part, by our small patient sample size. More extensive study of relatives, especially those who do not have the SCA1 mutation, would be very informative. More extensive study of relatives, especially those who do not have the SCA1 mutation, would be very informative. Whether there is truly a macular disorder associated with SCA1 awaits further study.

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Nonarteritic Anterior Ischemic Optic Neuropathy and Obstructive Sleep Apnea

Gorkem Bilgin, MD, FEBO, Yaran Koban, MD, Anthony C. Arnold, MD

Background: To evaluate the obstructive sleep apnea syndrome (OSAS) in patients with nonarteritic anterior ischemic optic neuropathy (NAION).

Methods: We recruited 27 patients with NAION and 27 age-matched and sex-matched controls who also were similar for systemic risk factors such as diabetes mellitus, hypertension, and hypercholesterolemia. All patients and controls underwent overnight polysomnography for the diagnosis of OSAS and calculation of apnea-hypopnea index (AHI).

Results: Patients and controls were statistically similar in terms of age, sex, gender, smoking, systemic risk factors, neck circumference, and body mass index. The subjects with AHI $\geq 20$ were accepted as OSAS. Fifteen of 27 patients (55.6%) with NAION and 6 of 27 controls (22.2%) had OSAS ($P < 0.05$).

Conclusion: The prevalence of OSAS was higher in patients with NAION, and the difference between patient and control groups was statistically significant ($P < 0.05$). This result supports prior series suggesting the association between NAION and OSAS.

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Obstructive sleep apnea syndrome (OSAS) is a common yet underdiagnosed condition that may be associated with significant morbidity if left untreated. It is characterized by recurrent interruption of normal breathing during sleep, owing to upper airway obstruction (apneic spells) (4). The apneic spells can cause a decrease in the arterial oxygen saturation and an increase in the carbon dioxide saturation during sleep. OSAS has been associated with an increased risk of cardiovascular disease, hypertension (HT), and stroke (5–7). We evaluated the possible association between OSAS and NAION.

METHODS

This prospective study involved 27 patients with NAION who were evaluated within 1 month of symptom onset. The control group consisted of 27 age- and sex-matched subjects with similar systemic risk factors for disorders such as diabetes mellitus, HT, and hypercholesterolemia. This study followed the tenets of the Declaration of Helsinki, and informed consent was obtained from all subjects. The study was approved by the Erzurum Regional Education and Research Hospital Ethical Committee and Review Board.

The diagnosis of NAION was made based on the following criteria:
1. Sudden onset of painless visual acuity and/or visual field loss
2. Diffuse or sectoral optic disc edema
3. Presence of relative afferent pupillary defect
4. Lack of clinical findings suggesting another disorder.

Polysomnography

Participants underwent overnight polysomnography (PSG) recordings in 2 sleep laboratories. Sleep was continuously recorded on a computerized system (Grass Technologies, West Warwick, RI) scored in 30-second epochs according to the American Academy of Sleep Medicine standardized criteria (8). PSG measurements included electroencephalograms

Nonarteritic anterior ischemic optic neuropathy (NAION) is a common cause of visual loss from optic nerve dysfunction. It is characterized by sudden or rapidly progressive, monocular or binocular visual decline, initially accompanied by segmental or diffuse optic disc edema, and later optic atrophy and retinal arteriolar narrowing (1,2). NAION is thought to result from circulatory insufficiency within the optic nerve head, but the specific mechanism and location of the vasculopathy remain unknown (3).
(EEG; C3-A2, C4-A1, O1-A2, O2-A1, F3-M2, F4-M1), right and left electrooculograms, mental-submental electromyogram (EMG), electrocardiogram, leg EMG, thoracic and abdominal wall motion (respiratory inductance plethysmography), pulse oximetry, combined nasal/oral thermistor, and a body position detector. Apnea during sleep was defined as cessation of airflow (90% fall in the amplitude of airflow signal compared to the baseline airflow) lasting at least 10 seconds. Hypopnea was defined as a 50% or greater fall in airflow lasting 10 or more seconds associated with a 3% or greater fall in oxygen saturation from baseline. The apnea-hypopnea index (AHI) was calculated using the total number of respiratory events (apneas and hypopneas) per hour sleep (9). Subjects with an AHI ≥20 were regarded as having OSAS.

Statistical Analysis

Means were compared by Student t test or Mann-Whitney U test. Prevalence of OSAS in patients with NAION was compared with the matched controls using Fisher exact test. Comparison of the clinical and PSG characteristics of the patients with NAION and matched controls was performed using the unpaired t test or Fisher exact test. SPSS version 17.0 for Windows (SPSS, Inc, Chicago, IL) was used for statistical analysis. Significance was accepted for P < 0.05.

RESULTS

Mean age of the patients with NAION and matched controls were 64.9 ± 7.86 years and 63.7 ± 5.24 years, respectively. There were no statistically significant differences with regard to age, gender, systemic risk factors, smoking, neck circumference, and body mass index between the 2 groups (P > 0.05). These data are summarized in Table 1. Fifteen of 27 patients (55.6%) with NAION and 6 of 27 subjects (22.2%) in the control group met the criteria for OSAS (AHI ≥20); the difference was statistically significant (P < 0.05, Fisher exact test). Relative risk for sleep apnea in NAION patients was 2.5 compared to the subjects in the control group.

TABLE 1. Clinical characteristics of patients with NAION and control group

<table>
<thead>
<tr>
<th></th>
<th>Patients With NAION (n = 27)</th>
<th>Controls (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD (y)</td>
<td>64.9 ± 7.86</td>
<td>63.7 ± 5.24</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>15 (55.6)</td>
<td>15 (55.6)</td>
</tr>
<tr>
<td>Female</td>
<td>12 (44.4)</td>
<td>12 (44.4)</td>
</tr>
<tr>
<td>Smoking</td>
<td>15 (55.6)</td>
<td>14 (51.9)</td>
</tr>
<tr>
<td>Body-mass index, mean ± SD (kg/m²)</td>
<td>28.9 ± 2.3</td>
<td>27.5 ± 3.6</td>
</tr>
<tr>
<td>Neck circumference, mean ± SD (cm)</td>
<td>35.97 ± 4.61</td>
<td>37.43 ± 3.78</td>
</tr>
<tr>
<td>Systemic disease, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (55.6)</td>
<td>14 (51.9)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>7 (26)</td>
<td>6 (22.2)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>12 (44.4)</td>
<td>10 (37)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>5 (19)</td>
<td>3 (11.1)</td>
</tr>
</tbody>
</table>

NAION, nonarteritic anterior ischemic optic neuropathy.

DISCUSSION

We found an increased prevalence of OSAS in patients with NAION. Several previous studies suggest the association. Hayreh (10) reported several patients with anterior ischemic optic neuropathy having a history of OSAS. Li et al (11) found that the prevalence of OSAS was 30% in 73 newly diagnosed patients with NAION and 17.8% in 73 age- and sex-matched controls. However, they used the survey of Sleep Apnea Scale of Disorders Questionnaire for the diagnosis of OSAS instead of PSG.

Mojon et al (12) recruited 17 patients with NAION, compared them with 17 age- and sex-matched controls, and performed overnight PSG on each patient. Twelve of 17 NAION patients (71%) and 3 of 18 controls (18%) had sleep apnea (P < 0.001). In this study, they used respiratory disturbance index (RDI) >10 in establishing the diagnosis of OSAS.

Arda et al (13) studied 20 patients with newly diagnosed NAION and 20 age- and sex-matched subjects with similar systemic risk factors for NAION as control group. All patients and controls underwent overnight PSG. Cases with an AHI >5 were accepted as having OSAS. The prevalence of OSAS was found to be 85% and 65% in the patient and control groups, respectively. There was no statistically significant difference between the 2 groups.

The diagnosis of OSAS is definitively established by nocturnal PSG (14). The definition of obstructive events is reported as AHI or RDI in PSG reports. AHI reflects the number of apneas and hypopneic episodes per hour of sleep (9). On the other hand, in addition to apneas and hypopneas, RDI includes breathing disturbances that are not included in the definition of apnea and hypopnea, that are abnormal without clear impact on oxygen saturation, or clear, visually recognizable EEG arousal (14). In other words, RDI can be higher or equal to AHI. OSAS severity is defined as mild for RDI ≥5 and <15, moderate for RDI ≥15 and ≤30, and severe for RDI >30 per hour (9).

In our study, we considered the subjects with an AHI ≥ 20 as having OSAS. Mojon et al (12) and Arda et al (13) accepted RDI >10 and AHI >5, respectively, as the threshold to diagnose OSAS, thus including subjects with mild or mild-moderate OSAS. Palombi et al (15) reported that 89% of 27 patients with newly diagnosed NAION had an AHI >15, concluding that NAION was nearly always associated with sleep apnea. We believe that by using more stringent criteria of AHI rather than RDI and a cutoff point of 20, we were able to reduce false-positive findings and provide a more accurate assessment of prevalence.
In conclusion, OSAS should be considered as a significant risk factor for NAION. Because there is no proven treatment for NAION, control of risk factors may be important in preventing involvement of the second eye. At this point, PSG should be considered in every patient with newly diagnosed NAION.

REFERENCES
A Resting State Functional Magnetic Resonance Imaging Study of Patients With Benign Essential Blepharospasm

Bo Zhou, Jinyu Wang, Yulan Huang, Yousong Yang, Qiyong Gong, Dong Zhou

Background: Benign essential blepharospasm (BEB) is a neurologic disorder characterized by an adult-onset focal dystonia that causes involuntary blinking and eyelid spasms. The pathophysiology of BEB patients remains unclear. This study investigated intrinsic low-frequency fluctuation in BEB patients during resting state functional magnetic resonance imaging (fMRI).

Methods: The study included 9 patients with BEB (mean age, 61.7 years; range, 52–66 years), in whom the average duration of symptoms was 2.7 ± 1.8 years, and another 9 subjects from an age- and sex-matched control group. Resting state fMRI was performed in both the patients with BEB and the normal controls. Voxel-based analysis was used to characterize the alteration of amplitude of low-frequency fluctuation (ALFF) in both patients with BEB and the normal controls.

Results: The whole brain analysis indicated that in comparison with the normal control group, there was a significantly increased ALFF in the left putamen, pallidum, insular lobe, and medial prefrontal cortex and a significantly decreased ALFF in the bilateral somatosensory regions, thalamus, cerebellum, and medial and posterior cingulate cortex.

Conclusion: The present study suggests that both an abnormal default mode network and corticostriatopallidothalamic loop may play a role in the pathophysiology of BEB.

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Benign essential blepharospasm (BEB) is an adult-onset focal dystonia that causes involuntary blinking and eyelid spasms (1). Conventional neuroimaging methods, including magnetic resonance imaging (MRI), do not consistently show any structural abnormalities in patients with BEB. Studies using positron emission tomography (PET) (2,3) and magnetic resonance spectroscopy (4) have demonstrated abnormalities of basal ganglia and thalamic functioning in patients with BEB, and PET also showed hypoactivity in cortical areas controlling the eyelids and hyperactivity in the pons and cerebellum (5). Using functional MRI (fMRI), Schmidt et al (6) showed that the episodes of involuntary eyelid spasms in BEB patients correlate with an increased striatal activation, while Baker et al (7) demonstrated cortical and subcortical circuit abnormalities. Although these studies suggest that dysfunction in both the basal ganglia and cortical areas may be associated with BEB, the pathophysiology of this disorder remains poorly understood.

Recently, there has been an increasing interest in the investigation of default mode of brain function. Through numerous neuroimaging studies (8–11), there is general consensus that default mode is a specific, anatomically defined brain system that is preferentially active when individuals are not focused on the external environment. This system is composed of the posterior cingulate cortex (PCC)/precuneus, ventral anterior cingulate cortex (vACC)/medial prefrontal cortex (mPFC), inferior parietal lobe (IPL), and lateral and medial temporal structures. These regions constitute a default mode network (DMN) with close functional connectivity (12–16).

Synchronous low-frequency fluctuation (LFF) in resting state fMRI has been extensively used to study spontaneous low-frequency neuronal activities. Some studies have suggested that the LFFs of blood oxygenation level–dependent (BOLD) fMRI signals are closely related to spontaneous neural activity (17–19). Although functional connectivity analysis can provide us with additional information of brain region networks, it does not reveal the BOLD signal change in regional spontaneous activity. Moreover, the detection of abnormal connectivity among brain regions does not tell us precisely the area of the brain with spontaneous abnormal

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activity. Biswal et al (20) developed an index called the amplitude of LFF (ALFF), for detecting the regional intensity of spontaneous fluctuations in BOLD signals, in which the square root of the power spectrum was integrated in a low-frequency range (<0.08 Hz). ALFF has already been used to study attention-deficit hyperactivity disorder (20,21), early stages of Alzheimer disease (22), and epilepsy (23). To our knowledge, there have been no studies of ALFF in BEB.

We first analyzed intrinsic LFF in BEB patients during resting state by applying ALFF and then compared ALFF between BEB patients and normal controls. We hypothesized that BEB patients may have different ALFF in some brain areas in comparison with normal controls.

MATERIALS AND METHODS

Subjects
This study analyzed 18 individuals including 9 patients with BEB and 9 normal volunteers from the Department of Neurology, West China Hospital, Sichuan University and the Sichuan Provincial People’s Hospital in Chengdu. There were 2 men and 7 women with BEB, with a mean age of 61.7 years (range, 52–66 years). The average duration of symptoms was 2.7 ± 1.8 years. Two patients received botulinum toxin injections 6 months before the study, but symptoms recurred after 3 months. Patient met the following inclusion criteria: 1) BEB, 2) no previous neuroleptic medication, 3) no other neurologic or psychiatric disease, 4) normal MRI brain scan, and 5) right-handedness according to the Edinburgh Handedness Inventory (24). Normal controls included 4 men and 5 women in the same age range, all of whom were right-handed and not taking psychotropic drugs. All 18 participants gave their written informed consent according to the Declaration of Helsinki, and the study protocol was approved by the local ethics committee.

Image Acquisition
Experiments were performed on a 3.0-T GE-Signa MRI scanner (EXCITE; General Electric, Milwaukee, WI) in Huaxi MR Research Center (West China Hospital, Sichuan University, Chengdu, China). Foam padding was used to minimize head motion for all subjects. Functional images were acquired using a single-shot, gradient-recalled echo planar imaging sequence (relaxation time [TR] = 2000 milliseconds, echo time [TE] = 30 milliseconds, and flip angle = 90°). Thirty transverse slices (field of view [FOV] = 24 cm, in-plane matrix = 64 × 64 mm, slice thickness = 5 mm, without gap, and voxel size = 3.75 × 3.75 × 5 mm), were acquired and aligned along the anterior commissure-posterior commissure line. For each subject, a total of 205 volumes were acquired, and the first 5 volumes were discarded to ensure steady-state longitudinal magnetization. Subjects were instructed simply to rest with their eyes closed without falling asleep and thinking of nothing. Subsequently, for spatial normalization and localization, a set of high-resolution T1 anatomical images was acquired in axial orientation using a 3-dimensional spoiled gradient-recall sequence (TR = 8.5 milliseconds, TE = 3.4 milliseconds, flip angle = 12°, matrix size = 512 × 512 × 156, and voxel size = 0.47 × 0.47 × 1 mm³) on each subject.

Data Preprocessing
Data preprocessing was carried out using SPM2 software (http://www.fil.ion.ucl.ac.uk/spm). The 200 volumes were first corrected for the temporal difference and head-motion correction. If translational or rotational parameters in a data set exceeded ±1.5 mm or ±1.5°, the data set was excluded from the analysis. There was no significant difference in the magnitude of motion correction parameters between the 2 participant groups (P > 0.05). The functional images were realigned with the corresponding T1 volume and warped into a standard stereotaxic space at a resolution of 3 × 3 × 3 mm³, using the Montreal Neurological Institute echo-planar imaging template in SPM2. Subsequently, they were spatially smoothed by convolution with an isotropic Gaussian kernel (full width at half maximum [FWHM] = 8 mm).

ALFF Analysis
The ALFF analysis was carried out using the software of REST (http://resting-fmri.sourceforge.net). First, the time series was transformed to a frequency domain with a fast Fourier transform, and the power spectrum was obtained. Since the power of a given frequency is proportional to the square of the frequency component amplitude of the original time-domain series, the square root was calculated at each frequency of the power spectrum, and the average square root was obtained across low frequencies (0.01–0.08 Hz) at each voxel. This average square root was taken as the ALFF. For standardization purposes, the ALFF of each voxel was divided by the global mean ALFF value (25,26).

Statistical Analysis
The ALFF result with 1-sample t test was not demonstrative since it reflected all the brain regions with high LFF in addition to the default mode (26). Subsequently, the ALFF values of each group were analyzed using 2-sample t tests in SPM2, to compare the differences of the whole brain between each group of patients and controls. A statistical threshold of P < 0.001 (uncorrected) was used for an exploratory whole-brain analysis.

RESULTS
Within the 2-sample t test comparisons for the ALFF between BEB patients and controls, the patients showed increases in the ALFF within the left putamen, insular lobe, pallidum, and mPFC (Fig. 1; Table 1). The cerebellum, thalamus, posterior central gyrus, and the PCC showed decreased ALFF (Fig. 2; Table 2).
DISCUSSION

In our study, we found significant ALFF differences between BEB patients and normal controls. Some areas of the brain showed increased ALFF in the BEB group, including the left putamen, insular lobe, pallidum, and mPFC. Areas showing decreased ALFF in BEB included the cerebellum, thalami, medial and PCC, and somatosensory regions (Figs. 1, 2).

Our results are consistent with some, but not all, previous findings in BEB studies. Biswal et al (20) found that ALFF was higher in the gray matter than in the white matter. In addition, Kiviniemi et al (27) reported activation in the visual cortex because of LFFs at approximately 0.034 Hz using the power spectrum method, indicating that ALFF may detect regional spontaneous neuronal activity. These studies employed regional homogeneity (ReHo) method (28) and functional connectivity analysis (29), techniques quite different from our ALFF method. ReHo and functional connectivity analyses focus on the similarities of intraregional and interregional time series, respectively, while ALFF measures the amplitude of regional activity.

Fox and Raichle (10) have pointed out that activity in the DMN is highest during rest and reduced during cognitive activity. In all subjects, it comprises a large frontal area including vACC, mPFC, orbitofrontal cortex, PCC, IPL, and a temporal region involving the parahippocampal gyrus.

In the present study, we found a significantly increased ALFF in mPFC and a decreased ALFF in the PCC of BEB patients. This suggests that there were distinct differences in the DMN in BEB patients compared with normal controls.

There is growing evidence that both functional and structural changes in the sensory cortex of patients with primary dystonia play pivotal roles in the pathophysiology of this disorder. The severity of dystonia correlated with the amount of overactivity in the primary somatosensory cortex (SI) during dystonic movements in patients with writer’s cramp (30). Bilateral postcentral gyrus overactivity during whistling may be a functional correlate of altered somatosensory representation in patients with orofacial dystonia (31). MRI voxel-based morphometry disclosed an increase of gray matter indicative of structural remodeling in primary somatosensory areas of patients with focal hand dystonia (32). In the present study, we found significantly decreased activity in the somatosensory region during the resting state in BEB patients compared to controls. Whether fMRI showed postcentral hypoactivity in the resting state, as we demonstrated, or hyperactivity during orofacial motor execution, as reported by Dresel et al (31), the results indicate that the somatosensory cortex is involved in orofacial dystonia. The sensory trick, a so-called geste antagonistique

**TABLE 1.** Areas showing increased amplitude of low-frequency fluctuation in comparing BEB patients and normal controls

<table>
<thead>
<tr>
<th>Anatomical Region</th>
<th>Hemisphere</th>
<th>MNI Coordinates (x, y, z)</th>
<th>Brodmann’s Area</th>
<th>Cluster Size</th>
<th>T Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Putamen</td>
<td>L</td>
<td>-15, 6, -6</td>
<td>48</td>
<td>19</td>
<td>4.62</td>
</tr>
<tr>
<td>Pallidum</td>
<td>L</td>
<td>-9, 3, -6</td>
<td>25, 48</td>
<td>2</td>
<td>4.63</td>
</tr>
<tr>
<td>Insular lobe</td>
<td>L</td>
<td>-33, 21, 12</td>
<td>47, 48</td>
<td>45</td>
<td>5.46</td>
</tr>
<tr>
<td>Superior frontal</td>
<td>L</td>
<td>-18, 6, 54</td>
<td>8, 9, 10</td>
<td>112</td>
<td>8.33</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>18, 3, 51</td>
<td>8, 9, 10, 11, 10</td>
<td>106</td>
<td>5.75</td>
</tr>
<tr>
<td>Superior frontal, medial</td>
<td>L</td>
<td>0, 42, 39</td>
<td>8, 9, 10</td>
<td>44</td>
<td>4.86</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>6, 30, 45</td>
<td>8, 9, 10, 32</td>
<td>93</td>
<td>5.86</td>
</tr>
</tbody>
</table>

L, left hemisphere; R, right hemisphere; MNI, Montreal Neurological Institute echo-planar imaging.
such as touching or stroking the face periorbitally, can alleviate the symptoms of patients with blepharospasm (33) and even transiently modulate the blink reflex circuitry (34). These findings are further evidence that the somatosensory system is involved in the pathophysiology of this disorder.

Our study showed an increased ALFF in the left putamen and pallidum and decreased ALFF in bilateral thalami in the BEB group. A majority of the studies on BEB and other dystonias have demonstrated abnormal metabolism of both the thalamus and basal ganglia (35–38), consistent with our findings.

There are 2 pathways in the motor circuit of basal ganglia. The striatum sends inhibitory projections to the basal ganglia output nuclei (globus pallidus interna/substantia nigra, GPi/SNr), which is called the direct pathway. It also sends inhibitory projections to the globus pallidus externa (GPe), which in turn inhibits the subthalamic nucleus (STN) and GPi. The latter indirect pathway from the striatum through the GPe and STN functions in an opposite manner to the direct pathway. The output from the basal ganglia (GPi/SNr) is inhibitory and projects to motor and premotor cortices, brainstem, and thalamus (39). The basal ganglia play a role in modulating lid movements through the pallidal-thalamic and nigral-collicular output pathways. The inhibitory projection of the globus pallidus to the thalamus can significantly modulate cortical activity associated with blinking. Many reports support the hypothesis that disturbances in striatal control of the globus pallidus (and substantia nigra pars reticulata) may be responsible for the altered neuronal activity in dystonia (2,40–42). It has been proposed that an increased activity in the direct striatopallidal pathway inhibits the internal segment of the globus pallidus, resulting in an increased inhibitory synaptic activity in the medial globus pallidus and a reduced activity in pallidal output to the thalamus (1).

Using fMRI, Schmidt et al (6) reported that a subregion of the putamen was active during spasms in BEB patients but not active during voluntary blinks in normal subjects. Blaxton et al (43) thought that putamen activation had only been implicated in reflex eye blinks to air puffs and did not observe any striatal activation with voluntary eyelid movements. Schmidt et al (6) noted that unilateral or bilateral activation of the putamen correlated with eyelid spasms in 6 patients with BEB; these activations were reproducible after 2 years, although putamen activation was not observed during voluntary blinking in any of the control subjects. Thus, altered putamen function may be a critical component of BEB.

However, Suzuki et al (44) examined 25 patients with BEB following botulinum-A toxin injection using PET with 18-fluorodeoxyglucose (FDG). They found hyperactivity in the thalamus correlating with a trend of glucose hypermetabolism bilaterally in the putamen; yet there was no

<table>
<thead>
<tr>
<th>Anatomical Region</th>
<th>Hemisphere</th>
<th>MNI Coordinates (x, y, z)</th>
<th>Brodmann’s Area</th>
<th>Cluster Size</th>
<th>T Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalamus</td>
<td>L</td>
<td>−9, −12, 9</td>
<td>—</td>
<td>17</td>
<td>−3.84</td>
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<tr>
<td></td>
<td>R</td>
<td>6, −18, 3</td>
<td>—</td>
<td>26</td>
<td>−3.97</td>
</tr>
<tr>
<td>Cerebellum 6</td>
<td>L</td>
<td>−30, −60, −30</td>
<td>—</td>
<td>30</td>
<td>−4.52</td>
</tr>
<tr>
<td>Cerebellum crus 1</td>
<td>R</td>
<td>51, −69, −36</td>
<td>—</td>
<td>17</td>
<td>−3.91</td>
</tr>
<tr>
<td>Precuneus</td>
<td>L/R</td>
<td>−6, −60, 69</td>
<td>5, 7</td>
<td>30</td>
<td>−3.99</td>
</tr>
<tr>
<td>Post/precentral gyrus</td>
<td>L</td>
<td>−51, −9, −6</td>
<td>3, 4</td>
<td>18</td>
<td>−3.74</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>57, −12, 45</td>
<td>3, 4</td>
<td>10</td>
<td>−3.91</td>
</tr>
</tbody>
</table>

L, left hemisphere; R, right hemisphere; MNI, Montreal Neurological Institute echo-planar imaging.
significant difference in comparison to controls ($P < 0.01$, uncorrected). The hyperactivity in the thalamus was also observed with the depletion of sensory feedback. Suzuki et al (44) concluded that thalamic hyperactivation may be one of the primary causes of BEB, as hyperactivity of the striatum is sensory input dependent. Also using PET, Kerrison et al (45) found decreased glucose uptake in the thalamus of patients with BEB, consistent with the results of the present study of decreased thalamic ALFF. Possibly, thalamic dysfunction is the primary defect in BEB. This is supported by the reports of blepharospasm in association with bilateral thalamic infarcts (46) and unilateral blepharospasm caused by an ipsilateral thalamomesencephalic hemorrhage (47). MRI and single-positrion emission computed tomography demonstrated lesions of the basal ganglia, the thalamus, or both in 5 of 7 patients with Meige syndrome (37), suggesting that voluntary motor control and reciprocal activity in the basal ganglia and thalamocortical circuits are impaired. A study by Esmaeli-Gutstein et al (2) employing PET with 18-FDG displayed striatal and thalamic hyperactivity in patients with BEB. This enhanced glucose metabolism reflected either increased excitatory or inhibitory neuronal activity in these regions. Further investigation is required to clarify the different roles of the thalamus and striatum in the pathophysiology of BEB.

Our study showed decreased ALFF in the cerebellum of BEB patients, which is consistent with the previous findings in BEB patients (45). However, Suzuki et al (44) found significant hypermetabolism in the cerebellum of botulinum toxic incomplete suppression BEB patients. Hutchinson et al (5) reported with PET imaging that BEB patients exhibit hypermetabolism of the cerebellum and pons during wakefulness but not during sleep. Ceballos-Baumann et al (48) found that in patients with writer’s cramp, cerebellar vermis activation was present before botulinum toxin administration but disappeared after the treatment. The cerebellum receives extensive somatosensory input via spinocerebellar pathways and processes sensory input (49). The abnormal metabolism in the cerebellum appears to be a secondary phenomenon related to muscular activity of the eyelids (6), probably not specific for BEB.

There are a number of limitations to our study. First, it is difficult to ask participants lying in a machine creating a good deal of noise to close their eyes with thinking of nothing. Second, the small sample size limits the generalization of our results. Third, 2 of our BEB patients had been treated with botulinum injections. Although the injections occurred 6 months before fMRI examination, it cannot be assumed that botulinum injections did not affect the cortical and subcortical BOLD signals.

In conclusion, the resting state fMRI in BEB patients revealed deficient ALFF of the cerebellum, thalamo-, somatosensory region, and PCC and increased ALFF of the left putamen, pallidum, and mPFC. This suggests that an abnormal DMN and corticostriatopallidothalamic loop may be associated with the pathophysiology of BEB. Evaluating BEB patients with electromyography during fMRI could lead to better model functions and determine both the role and activation sequence of cortical and other subcortical areas in the neural network underlying BEB.

REFERENCES


A Prospective Photographic Study of the Ocular Fundus in Obstructive Sleep Apnea

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Background: The prevalence of optic nerve and retinal vascular changes within the obstructive sleep apnea (OSA) population are not well-known, although it has been postulated that optic nerve ischemic changes and findings related to an elevated intracranial pressure may be more common in OSA patients. We prospectively evaluated the ocular fundus in unselected patients undergoing overnight diagnostic polysomnography (PSG).

Methods: Demographic data, medical/ocular history, and nonmydriatic fundus photographs were prospectively collected in patients undergoing PSG at our institution and reviewed for the presence of optic disc edema for which our study was appropriately powered a priori. Retinal vascular changes were also evaluated. OSA was defined using the measures of both sleep-disordered breathing and hypoxia.

Results: Of 250 patients evaluated in the sleep center, fundus photographs were performed on 215 patients, among whom 127 patients (59%) had an apnea/hypopnea index (AHI) ≥15 events per hour, including 36 with severe OSA. Those with AHI <15 served as the comparison group. None of the patients had optic disc edema (95% confidence interval [CI]: 0%–3%). There was no difference in rates of glaucomatous appearance or pallor of the optic disc among the groups. Retinal arteriolar changes were more common in severe OSA patients (odds ratio: 1.09 per 5 unit increase in AHI; 95% CI, 1.02–1.16; P = 0.01), even after controlling for mean arterial blood pressure.

Conclusions: We did not find an increased prevalence of optic disc edema or other optic neuropathies in our OSA population. However, retinal vascular changes were more common in patients with severe OSA, independent of blood pressure.

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Obstructive sleep apnea (OSA) is a condition consisting of intermittent upper airway obstruction during sleep, leading to periods of hypoxia, hypercapnia, and acute hypertension (1). It has been hypothesized that in OSA, physiological changes secondary to hypoxia can result in retinal ischemia and associated retinal vascular changes (2) and progression of glaucomatous damage to the optic nerve (3). In one large, recently published evaluation of billing records (4), an increased risk of nonarteritic anterior ischemic optic neuropathy (NAION) and idiopathic intracranial hypertension (IIH) was reported in patients with untreated OSA, leading the authors to conclude that OSA patients should undergo ophthalmologic screening (4). Their findings mirror another study, which concluded that early screening for potentially blinding optic neuropathies in patients with moderate to severe OSA is worthwhile from an economic standpoint (5). However, the risk for various ocular disorders among patients with OSA remains unclear, particularly because in prior studies, the retinal assessment was performed remote from the time of polysomnography (PSG) (up to 3 years), and optic disc appearance was not assessed (2). Additionally, these studies did not adequately control for potential confounders of these associations, such as obesity and hypertension. Our primary aim...
was to prospectively examine for optic disc edema among OSA patients at the same time as routine diagnostic PSG. Our secondary aim was to evaluate other optic disc, retinal, or vascular changes at the posterior pole of OSA patients recruited prospectively.

METHODS

Adult patients presenting to our Sleep Center for diagnostic PSG between July and December 2011 were eligible. Patients with known condition other than OSA that could cause raised intracranial pressure (ICP) were excluded. Informed consent was obtained. The study was approved by the Emory University Institutional Review Board and followed the tenants of the Declaration of Helsinki. An a priori sample size was calculated for the frequency of optic disc edema, our primary outcome, in order to set the precision of our estimate. Our sample size was based on exact 95% binomial confidence intervals (CIs) to produce an upper bound of no more than 3%, if no optic disc edema was found among the OSA patients, and a margin of error of less than 6% even if up to 10% of OSA patients had optic disc edema. Enrollment of at least 122 patients with OSA was required to achieve this level of precision.

Demographics

Demographic details including age, sex, ethnicity, and body mass index (BMI) were recorded. A review of ocular and medical history, including previously diagnosed hypertension and measurement of blood pressure, was conducted.

Polysomnography

All patients underwent conventional, laboratory-based, overnight PSG with monitoring of electroencephalography, electrocortilography, surface electromyography, and electrocardiography. Breathing was measured with separate channels for oral/nasal airflow, nasal pressure, thoracic and abdominal respiratory effort, and pulse oximetry. All recordings were made using Embla N7000 digital PSG using Remlogic software (Denver, CO), and they were scored by Registered Polysomnographic Technologists (6) and reviewed by sleep medicine certified specialists who were unaware of the results of ocular fundus evaluation. Apneas were scored as >90% reduction in respiratory airflow for at least 10 seconds. Hypopneas were defined as a diminution in airflow of at least 50% from the preceding baseline accompanied by at least 4% fall in oxygen saturation. The total number of apneas and hypopneas were summed and divided by the total sleep time in hours and multiplied by 60 to yield an apnea/hypopnea index (AHI), as a rate per hour of sleep. We also defined hypoxic burden as the percentage of the sleep time in which the pulse oximetry decreased below 90%.

Using these definitions for breathing events, we defined the presence of sleep apnea as an AHI of ≥15 events per hour. Individuals exceeding this threshold were compared to those with AHI<15 as an initial comparison. We then performed subgroup analyses in which individuals with severe sleep apnea (AHI ≥ 20 and hypoxic burden ≥ 10%) were compared with a subgroup with minimal AHI (<5) and minimal burden (<2%). For individuals undergoing split night studies (studies in which the first part of the night was done at baseline and the second part to perform continuous positive airway pressure titration), we used PSG data from only the diagnostic portion of the recording to generate these values.

Fundus Photography

Photographs centered at the optic disc and macula, from each eye, were obtained by an ophthalmologist, using a commercially available tabletop nonmydriatic ocular fundus camera (Kowa Nonynx α-D III; Kowa Optimed, Inc, Torrance, CA). All included patients had photographs taken on both eyes when they arrived at the sleep center around 8 PM. Two neuro-ophthalmology–trained investigators systematically reviewed the photographs of each eye for an a priori agreed upon set of findings, without the knowledge of the PSG results. The eye with the highest quality image (7) was used for the measurements of continuous variables (fractal analysis, cup-to-disc ratio); if both were of the same quality, the image from the right eye was used. In cases of asymmetrical findings (i.e., disc edema or retinal findings), the most abnormal eye was chosen for analysis. In cases of asymmetrical disc cupping, a label of glaucoma suspect was given. The disc appearances for each patient were assessed for edema, pallor, and glaucomatous changes (i.e., increased cup-to-disc ratio, focal neuroretinal rim notching). Retinal vascular changes for each patient were classified according to the classification of hypertensive changes (8) with “mild retinopathy” consisting of arteriolar narrowing, arteriolar sclerosis, arteriovenous nicking, “moderate retinopathy” including retinal nerve fiber layer (RNFL) hemorrhages, exudate or cotton wool spots, and “malignant” including associated disc swelling. In the case of disagreement regarding any of these findings, a third neuro-ophthalmologist made the determination of whether an abnormality was present or absent. Any other ocular abnormalities were also recorded. Patients with poor quality fundus photographs were excluded.

Fractal Analysis

The best fundus photograph from one eye was chosen for each patient and analyzed with ImageJ (National Institutes of Health, Bethesda, MD). An automated approach was used to extract the retinal vessels (Fig. 1). Specifically, we measured the fractal dimension and lacunarity of the retinal vasculature using the box-counting method (FracLac, Charles Sturt University, Australia), an established method of measuring structures that are not perfectly self-similar (9).
**Statistical Analysis**

The groups were compared using Wilcoxon rank sum test for continuous data, Fisher exact test for categorical data, and Mantel-Haenszel $\chi^2$ test for stratified categorical data. Linear regression was used to evaluate the relationship between continuous variables and AHI. Logistic regression was used to evaluate and control for potential confounding (using a 10% change in coefficient rule) by age, race, and BMI on the association between OSA and retinal vascular changes. Significance was set at the 0.05 level.

**RESULTS**

Two hundred fifty patients presented for overnight sleep studies when digital fundus photography was available. Of the 250 patients, 215 were enrolled (excluded: 15 refused, 5 unable to consent, 3 photographs of poor quality, and 2 craniosynostosis with possible increased ICP). There were no other exclusions; in particular, no patients had been referred for sleep studies during this period with a possible diagnosis of IIH or NAION. One hundred twenty-seven patients (59%) had OSA, based on AHI $\geq 15$. Among those patients with an AHI $\leq 15$, diagnoses were subclinical sleep-disordered breathing ($n = 52$), primary snoring ($n = 16$), periodic leg movement disorder ($n = 12$), physiologic hypersomnolence ($n = 4$), repetitive intrusions of sleep ($n = 1$), and normal ($n = 1$).

Relative to the comparison group, OSA patients were older, more likely to be men, had a higher BMI, and were more likely to have a previous diagnosis of hypertension (Table 1). There was no difference in the measured mean systolic blood pressure and mean arterial blood pressure (MAP) comparing OSA patients relative to the comparison group, but severe OSA patients (AHI $\geq 20$; hypoxic burden $\geq 10\%$) had higher mean blood pressures when compared to the minimal AHI/minimal hypoxic burden group (AHI $< 5$; burden $< 2\%$) patients. There were no differences comparing race or frequency of diagnosed diabetes mellitus.

No patient had an optic disc appearance suspicious for optic disc edema. There were no differences in glaucomatous optic disc appearances between OSA and the comparison group (5% vs 2%; $P = 0.84$; odds ratio [OR] = 1.46; 95% CI, 0.32–6.75 controlling for age, race, sex, hypertension, and diabetes; logistic regression), and the rates of clinical diagnosis of glaucoma or glaucoma suspect were equal between the 2 groups. The rates of sectoral disc pallor were low and equal between the groups.

There were more retinal vascular changes, similar to those seen in mild hypertensive retinopathy (9), in severe OSA patients vs minimal AHI/minimal hypoxic burden patients (Fig. 2). These arteriolar changes remained more common in severe OSA patients even after controlling for the history of diagnosed hypertension: (hypertensive severe OSA vs hypertensive minimal AHI/minimal hypoxic burden: 33 vs 8%; nonhypertensive severe OSA vs nonhypertensive minimal AHI/minimal hypoxic burden: 28 vs 9%; $P = 0.04$). AHI remained an independent predictor of retinal arteriolar changes (OR, 1.09 per 5 unit increase in AHI; 95% CI, 1.02–1.16; $P = 0.01$) even after controlling for measured MAP (OR, 1.99 per 10 mm Hg increase; 95% CI, 1.38–2.88; $P = 0.0003$). For example, for any given blood pressure, an AHI $> 40$ conferred a doubling of the odds of retinal vascular changes being seen, compared to a patient with AHI $< 5$. These relationships were not confounded by age, race, or BMI based on multivariable logistic regression. None of the comparison group had RNFL hemorrhages compared to 4% of the OSA patients ($P = 0.08$), which would be classified as moderate hypertensive changes. Of these 5 patients, one had known diabetes with hypertension, 2 had a diagnosis of hypertension, and 2 had neither.

Fractal analysis of the retinal vascular tree found no differences in any measure of fractal dimension or lacunarity between the OSA patients and the comparison group ($P = 0.16$; Table 1; Fig. 1).

**DISCUSSION**

We evaluated 215 patients undergoing PSG, 127 with OSA, in what is, to our knowledge, the largest systematic
investigation of the ocular fundus findings of OSA patients on the night of PSG.

Episodic ICP elevations occur during apneic episodes of the OSA patients (10). In addition, hypercapnia can alter cerebral vascular reactivity, causing an increased ICP with the potential for associated optic disc edema (11,12). Hypoxia can also occur during apneic episodes, and subjects with hypoxia at high altitude have been shown on fundus photography to develop disc edema, markedly tortuous retinal vasculature, and preretinal hemorrhages (13). Of 41 OSA patients examined in one study (5), 2 were found to have “disc swelling,” but no further comment was made about these patients because the study was designed to screen for glaucoma. Another study examined 35 OSA patients and found no optic disc edema (14). Similar to this latter study, we found no optic disc edema in our 127 OSA patients (0%; 95% CI, 0%–3%).

TABLE 1. Comparison of the demographics, medical and ocular history, and ocular fundus photography findings among patients evaluated for obstructive sleep apnea

<table>
<thead>
<tr>
<th></th>
<th>Overall Comparison</th>
<th>Subset Analysis</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>OSA* (n = 127)</td>
<td>Severe OSA† (n = 36)</td>
</tr>
<tr>
<td></td>
<td>Comparison† (n = 88)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>AHI* (±SD)</td>
<td>37 (±29)</td>
<td>57 (±31)</td>
</tr>
<tr>
<td>Hypoxic burden, % (±SD)</td>
<td>13 (±20)</td>
<td>32 (±26)</td>
</tr>
<tr>
<td>Age, years (±SD)</td>
<td>60 (±12)</td>
<td>60 (±12)</td>
</tr>
<tr>
<td>Sex</td>
<td>62% men</td>
<td>58% men</td>
</tr>
<tr>
<td>Race</td>
<td>59% white</td>
<td>39% white</td>
</tr>
<tr>
<td>Body mass index, kg/m² (±SD)</td>
<td>32 (±8)</td>
<td>28 (±8)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>49% (62)</td>
<td>50% (18)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg (±SD)</td>
<td>134 (±16)</td>
<td>138 (±18)</td>
</tr>
<tr>
<td>Mean arterial blood pressure, mm Hg (±SD)</td>
<td>96.5 (±11) 95.7 (±11)</td>
<td>99.6 (±12) 93.6 (±10)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>17% (21)</td>
<td>19% (7)</td>
</tr>
<tr>
<td>Optic disc edema</td>
<td>0% (0)</td>
<td>0% (0)</td>
</tr>
<tr>
<td>Glaucomatous discs</td>
<td>5% (6)</td>
<td>13% (5)</td>
</tr>
<tr>
<td>Diagnosis glaucoma</td>
<td>3% (4)</td>
<td>8% (3)</td>
</tr>
<tr>
<td>Glaucoma suspect</td>
<td>2% (2)</td>
<td>6% (2)</td>
</tr>
<tr>
<td>Sectoral pallor</td>
<td>2% (2)</td>
<td>6% (2)</td>
</tr>
<tr>
<td>Retinal vascular changes</td>
<td>17% (21)</td>
<td>31% (11)</td>
</tr>
<tr>
<td>RNFL hemorrhages</td>
<td>4% (5)</td>
<td>6% (2)</td>
</tr>
<tr>
<td>Fractal dimension</td>
<td>0.0014</td>
<td>0.0016</td>
</tr>
<tr>
<td>Lacunarity</td>
<td>1.46</td>
<td>1.47</td>
</tr>
</tbody>
</table>

*OSA defined as AHI ≥ 15.
†Comparison defined as AHI ≥ 5 and hypoxic burden (cumulative time with SaO₂ < 90%) ≥ 10% of recording.
§Minimal burden: defined as AHI < 5 and hypoxic burden (cumulative time with SaO₂ < 90%) < 2% of recording.
RNFL, retinal nerve fibre layer.

FIG. 2. Fundus photography of a patient with obstructive sleep apnea. A. Arteriovenous nicking (arrow) and focal arteriolar narrowing (arrowheads). B. Arteriolar sclerosis and narrowing (arrow). C. Arteriolar narrowing (arrow).
Other optic neuropathies have been associated with OSA. In the case of glaucoma, the findings have been contradictory, with one study showing no difference (15) and another reporting rates nearly 4 times higher than the expected population rate of 2% (3). Studies of NAION patients have found that 71%–89% have OSA by diagnostic PSG compared to 18% of controls (16), but whether the association between OSA and NAION is only because of confounding by shared risk factors for both conditions (e.g., age) or truly represents a causal relationship between OSA and NAION remains unknown. In our study, we found no differences between the optic disc appearance of patients with OSA compared to those without OSA, and we found no differences in the frequency of disc pallor or diagnosed glaucoma between the 2 groups.

The only difference we demonstrated was that retinal vascular changes, similar to those seen in mild hypertensive retinopathy, were over 3 times more common in severe OSA patients than in the minimal AHI/minimal hypoxic burden patients, even after controlling for diagnosed hypertension. The odds of retinal vascular changes also increased with increasing AHI, even when controlling for the patients’ measured blood pressure, age, race, and BMI. Previous fundus photographic studies have shown that retinal vascular changes are associated with hypertension (17) but not sleep-disordered breathing (2). Therefore, one potential explanation for our observations is that the vascular changes are caused by elevated blood pressure and are exacerbated by the presence of OSA. However, the changes seen could instead be the result of the OSA and exacerbated by hypertension. As in any observational study, residual confounding from the use of a single blood pressure measurement or from unknown or unmeasured confounders could also explain our results. Selection bias is also a concern because it is likely that hypertension and its comorbidities play a role in which patients are referred for sleep studies.

Various human studies have shown that retinal, but not choroidal, blood flow is affected by hypercapnia (18,19), and oxygen saturation does not affect the flow in either ocular circulation (19). However, if OSA causes chronic physiological changes in blood flow, this may lead, over time, to the visible arteriolar changes we documented on fundus photography, independent of elevated blood pressure. Indeed, OSA has been shown to be an independent risk factor for other conditions associated with vascular changes, such as stroke, heart disease (20), and impaired renal function (21). Vascular endothelial dysfunction has been documented in OSA patients, which is independent from hypertension (22). The arteriolar changes we found on fundus photography may be a visible evidence of the end organ damage produced by OSA.

Fractal analysis is used in the spatial analysis of branching patterns in biological systems (23), including cardiovascular disease (24) and the retinal vasculature in patients with hypertension (6). However, our fractal analysis failed to show any of the subclinical changes in the overall branching patterns of the retinal vasculature that have been described in larger studies of hypertensive retinopathy (8,24). We acknowledge that our study may be relatively underpowered for this outcome, particularly for detecting subtle differences in retinal fractal analysis.

In conclusion, our study showed that arteriolar changes are more common in severe OSA patients than in those with no OSA. We did not find evidence of differences in the prevalence of glaucomatous changes or optic disc edema. Our results do not support the routine ophthalmoscopic screening of OSA patients for optic neuropathies. However, if our finding of retinal arteriolar changes as an independent association with OSA is confirmed, evaluation of the retinal vasculature may help inform future studies of the pathophysiology of end organ damage in OSA.

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Acquired Oculomotor Nerve Paresis with Cyclic Spasms in a Young Woman, a Rare Subtype of Neuromyotonia

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Background: To report an unusual case of cyclic oculomotor nerve paresis and spasms, which developed 5 years following brain radiotherapy for cerebellar medulloblastoma.

Methods: Observational case report.

Results: The cyclic oculomotor nerve paresis and spasms resolved in our patient when treated with carbamazepine. However, because of severe photophobia and tearing, carbamazepine had to be discontinued leading to reappearance of the eye movement disorder.

Conclusion: Cyclic oculomotor nerve paresis and spasms appear to be a delayed effect of radiotherapy and respond to carbamazepine therapy. It may be a rare form of ocular neuromyotonia.


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Ocular neuromyotonia (ONM) is an acquired disorder characterized by brief episodic contractions of muscles supplied by the oculomotor, trochlear, or abducens nerves resulting in paroxysmal strabismus and diplopia (1–5). It usually is associated with a history of previous radiation therapy to the parasellar region (3–6). Cyclic oculomotor paresis and spasms (COPS) is a rare phenomenon, that is, usually congenital (7). Miller and Lee (8) described 2 patients with COPS, appearing years following irradiation of the skull base. They proposed that acquired COPS and ONM may be related phenomena with similar underlying mechanisms. We describe a young woman with acquired oculomotor paresis with cyclic spasms following brain radiotherapy and treated with carbamazepine.

CASE REPORT

A 34-year-old woman underwent resection of posterior fossa medulloblastoma followed by radiotherapy and chemotherapy. Five years later, she developed intermittent episodes of vertical and horizontal diplopia associated with intermittent incomplete closure of the left eyelid. Neuro-ophthalmologic examination, including extraocular movements, was normal except for episodes that cycled every 2–3 minutes of partial left oculomotor spasm alternating with paresis. During the paretic phase, the patient had left hypotropia and moderate limitation in adduction of the left eye. Neurological testing was otherwise normal except for mild ataxia.

Brain magnetic resonance imaging (MRI) with contrast showed no evidence of recurrent tumor and ictal and prolonged interictal electroencephalogram recordings were normal. Treatment with carbamazepine 400 mg daily completely relieved the eye movement disorder, but 2 years later, the patient developed severe photophobia and tearing. Carbamazepine was discontinued and the photophobia resolved but the abnormal ocular movements reappeared.

The episodes of involuntary eye movements leading to vertical and horizontal diplopia consisted of cyclic oculomotor spasms and paresis of the left eye. They lasted for 1–2 minutes, recurring every few hours spontaneously or provoked by focusing on an object (see Supplemental Digital Content, Video 1, http://links.lww.com/WNO/A74 [informed consent was sought and granted by the patient for the filming and publishing of the related video]). On occasion, there were episodes of forced adduction of the left eye with reduced eyelid opening (Fig. 1). Infrequent intermittent limitation of abduction of the left eye was observed (see Supplemental Digital Content, Video 2, http://links.lww.com/WNO/A75).
Therapeutic trials with oxcarbazepine, phenytoin, and lamotrigine failed to halt the abnormal eye movements. Carbamazepine was restarted with marked improvement but with the return of photophobia.

DISCUSSION

Almost all reported cases of COPS have occurred in children or adults with a longstanding history of ocular motor dysfunction (7). Adult patients with acquired COPS typically occur following an acquired oculomotor nerve palsy without a history of previous brain radiotherapy. The clinical profile of our patients fits closely to that reported by Miller and Lee (8). They described 2 patients who developed COPS following radiation for pituitary tumor and parasellar meningioma. Like our patient, they did not have an oculomotor nerve palsy prior to onset of COPS. One of their patients failed to improve on carbamazepine, whereas the other declined treatment. Given the spontaneous onset of the cyclic oculomotor disorder, and prior exposure to radiation therapy to the skull base, Miller and Lee postulated that while COPS differed from ONM, they likely shared similar pathogenic mechanism.

Although the etiology of COPS is unknown, Loewenfeld and Thompson (7) believed that the disorder is caused by damage to the intracranial portion of the oculomotor nerve, with retrograde degeneration of oculomotor neurons. This leads to unstable cell membranes resulting from segmental demyelination or microangiopathy (3), and the injured nerve generates spontaneous impulses, leading to involuntary contraction of the muscles innervated by the oculomotor nerve (4).

Our case appears unique. The clinical picture resembles COPS, in that the spasms were followed by a paretic phase, but between episodes, eye movements were normal. As in ONM, the episodes could be provoked by change in gaze while focusing on an object.

The clinical findings in our patient combining COPS with neuromyotonic characteristics and following radiation therapy makes it likely that both eye movement disorders share similar underlying mechanisms.

Although not a reported side effect in the literature, 12 cases of photophobia associated with carbamazepine are recorded in the data file of Novartis (Amos D. Korczyn, MD, personal communication, 2012). The fact that photophobia disappeared after treatment was halted and reemerged following rechallenge supports the conclusion that photophobia is a rare side effect of carbamazepine.

REFERENCES

Optic Disc Edema in an Astronaut After Repeat Long-Duration Space Flight


Background: A number of ophthalmic findings including optic disc edema, globe flattening, and choroidal folds have been observed in several astronauts after long-duration space flights. The authors report the first astronaut with previously documented postflight ophthalmic abnormalities who developed new pathological changes after a repeat long-duration mission.

Methods: A case study of an astronaut with 2 long-duration (6 months) exposures to microgravity. Before and after his first long-duration space flight, he underwent complete eye examination, including fundus photography. Before and after his second flight, 9 years later, he underwent fundus photography, optical coherence tomography, ocular ultrasonography, and brain magnetic resonance imaging, as well as in-flight fundus photography and ultrasound.

Results: After his first long-duration mission, the astronaut was documented to have eye findings limited to unilateral choroidal folds and a single cotton wool spot. During a subsequent 6-month mission, he developed more widespread choroidal folds and new onset of optic disc edema in the same eye.

Conclusion: Microgravity-induced anatomical changes that occurred during the first mission may have set the stage for recurrent or additional changes when the astronaut was subjected to physiological stress of repeat space flight.

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In 2011, a report from the Space Medicine Division of the National Aeronautic and Space Administration (NASA) described 7 astronauts who developed a spectrum of ophthalmic findings, including optic disc edema, globe flattening, choroidal folds, and hyperopic shifts in refraction, after long-duration space flights to the International Space Station (ISS) (1). After a 161-day mission, one of these astronauts had ocular findings of choroidal folds inferior to the disc and a single cotton wool spot, both in the right eye. The purpose of this report was to document the recurrence of choroidal folds and the new onset of unilateral disc edema in the right eye of the same astronaut after a second long-duration (193 days) space mission 9 years after his first flight. Postflight ophthalmic abnormalities were captured with photographic and imaging documentation. Given this patient’s normal postmission lumbar puncture (LP) opening pressure, we hypothesize that local ocular vascular or orbital optic nerve sheath changes associated with microgravity fluid shifts may have played a leading role in the etiology of these anomalies.

CASE REPORT

A 57-year-old astronaut flew his first long-duration mission to the ISS in 2003 and his latest mission in 2011–2012. Due to the relative likelihood of attributability of these data, the subject has provided written informed consent.

Before the first mission, his fundus examination was normal. During this mission, a decrease in near visual acuity


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starting about 6 weeks into the flight was his only complaint. Examination on return to Earth revealed large choroidal folds inferior to the optic disc of the right eye without macular involvement and a single cotton wool spot along the inferotemporal vascular arcade (Fig. 1). Examination of the left eye was normal, and there was no evidence of optic disc edema in either eye. The cotton wool spot resolved within a month, and while the choroidal folds gradually diminished, they were still present in fundus photographs 3 years later. No other studies were undertaken, but subsequent recognition of these findings in other astronauts led to the implementation of in-flight ultrasound and retinal imagery in 2009. In 2011, 6 months before the second mission, the astronaut still had choroidal folds in the right eye that were detectable only on optical coherence tomography (OCT) (Fig. 2).

On OCT, preflight retinal nerve fiber layer (RNFL) thickness was normal in both eyes. Preflight magnetic resonance imaging (MRI) showed a normal appearance of the brain, bilateral optic nerve sheath distention, and optic nerve tortuosity with mild right globe flattening. These findings were confirmed using preflight ultrasound. One month into the mission, ultrasound demonstrated an increase in optic nerve sheath diameter (ONSD) that persisted throughout the mission. Toward the end of the mission, the degree of right globe flattening increased and globe flattening developed in the left eye. Approximately 3 months into the flight, retinal and optic nerve head images were captured by real-time remotely guided video funduscopy and downlinked to Mission Control Center in Houston, Texas. There was recurrence of subtle choroidal folds in the same location in the right eye, and 2 months later, the choroidal folds were now seen with mild right optic disc edema (Fig. 3). Orbital ultrasound and MRI results are shown in Table 1. The data compiled in Table 1 are based on newly developed testing methods that have not been fully analyzed for accuracy and reliability.

Two days after the space mission, the right fundus showed Frisen grade 1 optic disc edema with choroidal folds above and below the disc (Fig. 4). The left fundus was normal. There was prominent RNFL thickening.
in the right eye, with normal thickness in the left eye (Fig. 5). At this time, axial length (IOL Master, Jena, Germany) decreased by 0.14 mm in the right eye and 0.13 mm in the left eye, compared to preflight measurements. MRI performed 6 days postflight confirmed the presence of bilateral globe flattening and a partial empty sella. Both MRI (Fig. 6) and ultrasound (Fig. 7) demonstrated a moderate increase in the ONSD compared to preflight, paradoxically, left eye > right eye (Table 1). An opening pressure of 18 cm of water was measured on LP 8 days after landing. Intraocular pressure averaged 12 mm Hg in each eye during the mission, compared to preflight and postflight measurements of 10 mm Hg. The astronaut noted no change in visual acuity during his second flight and in-flight distance, and near visual acuity testing was consistent with preflight. No complaints of headache, pulsatile tinnitus, or diplopia were noted during either flight. Cycloplegic refraction did not change after the second flight, and his vision remained correctable to 20/20 in each eye.

Fundus photographs taken 52 days postmission documented a normal optic disc in both eyes. RNFL thickness measured 52 days postflight returned to near normal (Fig. 5). It should be added that this astronaut had a short duration (16 days) Space Shuttle flight in 2008 between his 2 ISS missions and had thus spent a total of 370 days in space during a 9-year period.

**DISCUSSION**

During the past 7 years, the space agencies participating in the ISS program have intensified the medical surveillance of crew members. Ophthalmic procedures now include high-resolution

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**TABLE 1.** Measurements obtained with orbital ultrasound and magnetic resonance imaging during 193-day space mission

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Preflight</th>
<th>Inflight</th>
<th>Postflight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>US 11 mo</td>
<td>US 9 mo</td>
<td>US 6 mo</td>
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<td></td>
<td>MRI</td>
<td>US 1 mo</td>
<td>US 3 mo</td>
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<tr>
<td></td>
<td>US 5 mo</td>
<td>US 3 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MRI 6 days</td>
<td></td>
<td></td>
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<tr>
<td><strong>Right eye</strong></td>
<td></td>
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<tr>
<td>Ultrasound axial length</td>
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</tr>
<tr>
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<td>0.62</td>
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<tr>
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<tr>
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<td>1</td>
</tr>
<tr>
<td>Disk protrusion grade</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Sheath hypoechogenicity grade</td>
<td>0</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>Sheath inhomogeneity grade</td>
<td>0</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>Nerve tortuosity grade</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td><strong>Left eye</strong></td>
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<td>Sheath/nerve ratio</td>
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<tr>
<td>Disk protrusion grade</td>
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<tr>
<td>Sheath inhomogeneity grade</td>
<td>0</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>Nerve tortuosity grade</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

All measurements in centimeters. All grades determined as: 0 = none; 1 = mild; 2 = moderate; 3 = severe. Ultrasound axial length measurements are underestimated due to use of nonophthalmic scanner without adjustment for propagation speed.

MRI, magnetic resonance imaging; US, ultrasound.
fundus photography, cycloplegic refraction, ocular and optic nerve ultrasound, MRI of the brain and orbits, and retinal and optic nerve OCT. Using these tests, after approximately 6 months of continuous space flight, 7 astronauts were shown to have varying degrees of optic disc edema, globe flattening, choroidal folds, and hyperopic shifts in refraction (1). All changes were seen in men and were observed more frequently in the right eye. From the inception of the US Space Program through July 2012, a total of 47 American astronauts have completed long-duration (>30 days) space missions, and

**FIG. 4.** Right fundus findings 2 days after space mission. **A.** Mild optic disc edema is present with inferior choroidal folds (arrow). **B.** Scanning laser ophthalmoscope image demonstrates superior and inferior choroidal folds (arrows). **C.** Choroidal folds are shown with spectral domain optical coherence tomography on vertical scan obtained just nasal to the optic disc.

**FIG. 5.** Retinal nerve fiber layer (RNFL) thickness measured by optical coherence tomography: (A) preflight; (B) 2 days postflight; (C) 52 days postflight. OD, right eye; OS, left eye.
were repeat long-duration flyers. Since the implementation of ocular surveillance program of NASA in 2006, 27 US astronauts have flown long-duration missions. Of this group, 12 were found to have one or more of the ocular abnormalities observed in our case. Asymptomatic disc edema was also documented in 8 of 16 long-duration cosmonauts studied during the Russian Mir Space Station program (2).

Three possible mechanisms have been proposed to explain the ophthalmic findings. These are not mutually exclusive and may be multifactorial. The first possibility is that the ocular changes resulted from increased intracranial pressure (ICP). It is thought that venous stasis in the head and neck, produced by cephalad fluid shifts in microgravity, may cause impairment of cerebrospinal fluid (CSF) outflow and cerebral venous congestion, both of which could lead to a rise in ICP (1,3). Support for this hypothesis includes borderline high opening pressures in 2 of the astronauts described previously (1), an elevated ICP of 28.5 mm H₂O in one (1) and MRI evidence of moderate concavity of the pituitary gland in 3 astronauts (4). Also, it has been proposed that pre-existing chemical differences in some individuals, possibly associated with defects in the folate and vitamin B₁₂-dependent 1-carbon transfer pathway, which have little or no demonstrable effect under Earth-gravity conditions, may set the stage for pathological changes leading to an increase in ICP in prolonged microgravity exposure (5).

A rise in ICP could cause distension of the optic nerve sheaths, stasis of axoplasmic flow, axonal swelling, and optic disc edema. The magnitude of the difference between CSF pressure within the optic nerve sheath and intraocular pressure (IOP) across the lamina cribrosa (translaminar pressure difference) may also play a role (6). In some astronauts, this pressure difference may lead to increased nerve sheath volume and exert an anterior force that indents the posterior sclera, resulting in posterior globe flattening, decreased axial length, and choroidal folds. Although the LP opening pressure was normal in our patient 8 days after landing, no LP was performed preflight or during the mission, so the role of CSF pressure is problematic. Elevated ICP as the sole etiology is problematic. Elevated ICP as the sole etiology is not proven since: 1) not all of the measured postflight opening pressure on LP have been elevated, and most of those that were elevated were in the borderline range; 2) common symptoms seen in patients with idiopathic intracranial hypertension (IIH), such as headache, pulse-synchronous tinnitus, transient visual obscurations, and diplopia, have not been reported in astronauts; 3) choroidal folds, while a known finding in IIH, seem to be a more prominent finding in our patient cohort; and 4)

![Reconstructed sagittal and axial orbital T2 magnetic resonance imaging obtained with a 3 Tesla magnet. A. Oblique images preflight (pre) and 6 days postflight (post) demonstrate increased diameter of the optic nerve sheaths and distention of surrounding cerebrospinal fluid compartment. Posterior globe flattening is seen in preflight and postflight scans. B. Postflight T2 axial images show moderate flattening of the globes.](image)
the presence of cotton wool spots cannot be explained based on elevated ICP alone.

A second possible explanation of our findings is that the optic disc edema and other abnormalities are the result of localized events occurring at the level of the intracanalicular and intraorbital optic nerve that are independent of CSF pressure (1). In a 1-gravity (1 G) environment, it is assumed that there is homogeneity of both pressure and biochemical constituents of CSF throughout the subarachnoid space (SAS). However, the unique cul de sac-like anatomical connection between the intracranial SAS and the SAS of the optic nerve may create a fragile flow equilibrium that could be impacted by long-standing microgravity fluid shifts and optic nerve sheath compliance (7,8). The fluid shifts may cause alterations in CSF flow dynamics in the intraorbital portion of the SAS, such that CSF enters the SAS but outflow may be impeded (9,10). Perhaps, under prolonged microgravity conditions, CSF in the SAS of the optic nerve may gradually become partially or completely sequestered, producing a type of optic nerve compartment syndrome. The fact that our astronaut had a normal LP opening pressure in conjunction with severe bilateral enlargement of the ONSD lends support to this theory. Perhaps, slight anatomical differences between the intraorbital optic nerves and sheaths, which may be inconsequential at 1 G, become the salient features during extended microgravity and may account for the optic disc edema and disc edema asymmetry noted in previous astronauts, as well as the unilateral disc edema in this astronaut. In addition, microgravity-related changes in CSF flow within the intraorbital portion of the optic nerve may lead to biochemical changes in CSF that prove toxic to the optic nerve causing the cotton wool spot noted during our astronaut’s first mission (1).

Previous research conducted on the anatomy and CSF dynamics of the optic nerve sheath have some bearing on our findings. Hayreh (11) demonstrated that the capacity of the optic nerve sheath to expand during a rise in ICP varied along its length. The retrobulbar area expanded the most while the intracanalicular portion expanded the least. He also noted that elevated SAS pressure resulted in increased ONSD, even before papilledema appeared. Hansen and Helmke (12) showed that the optic nerve sheath expands rapidly in vivo after small pressure changes during intrathecal infusion tests. In isolated human optic nerves, changes from baseline sheath diameter occurred with as little as a 5 mm Hg increase in SAS fluid pressure (13). They demonstrated that even if SAS pressure is later reduced, a new baseline ONSD may persist. Our data suggest that, regardless of the specific mechanism of increased intrasheath pressure, a similar resetting of ONSD may have occurred during this astronaut’s first mission. The sheath may have remained enlarged after his return to the Earth after his first flight, and the distension process may have resumed during the second flight from an already expanded baseline.

A third possible etiology for the optic disc edema observed is ocular hypotony. Although no long-term studies of IOP in microgravity have been performed, some head-down bed rest (14,15) and postflight studies (16) suggest

**FIG. 7.** Ultrasound images taken 3 days postflight. A. Axial section of the right eye shows elevation of the disc area, nasal flattening of the posterior globe, and a tortuous optic nerve. The white line represents axial length. B. Oblique sagittal view of the same eye shows localized flattening of the posterior globe. C. Oblique axial section through the left eye. The bulbar segment of the sheath is markedly dilated (white line) and measured 0.79 cm (13 MHz linear array probe, depth of view 4 cm).
that a lowering of the IOP may occur during prolonged microgravity exposure (17). Ocular hypotony is known to cause disc edema, posterior globe flattening, choroidal folds, and a hyperopic shift in refraction (18,19). However, since this astronaut’s IOP during the mission remained near pre-flight values, this mechanism seems unlikely.

Regardless of the specific etiology, our documentation of more widespread choroidal folds and the new onset of optic disc edema after a second long-duration flight, 9 years after the first, suggest that for this astronaut the ocular effects of repeat space travel may have been cumulative. We speculate that the microgravity-induced anatomical changes that occurred during the first mission could have predisposed our astronaut to recurrent and additional changes when subjected to the physiological stress of repeat space flight. Continued preflight, in-flight, and postflight ophthalmic evaluation of astronauts will help determine the long-term clinical significance of these findings and whether the results seen in this astronaut are found in other repeat long-duration flyers.

REFERENCES


Low Prevalence of Bilateral (Presumed Nutritional) Optic Neuropathy as a Cause of Blindness in The Gambia

Abdirisak A. Dalmar, MD, PhD, Katherine E. Hodson, MSc, Gordon T. Plant, MD, FRCP, FRCOphth

Objective: Previous reports of epidemics of optic neuropathy in Africa have mainly focused on eastern and central areas. Our study aimed to measure the prevalence of optic neuropathy in The Gambia, a West African country, and compare this prevalence with a simultaneously occurring epidemic of optic neuropathy, now considered endemic, in Tanzania.

Methods: The sample population, derived from the Gambian National Blindness Survey (1996), was selected using simple random sampling. Thirty-three cases of low vision/blindness were identified where optic neuropathy was the sole cause of visual loss. Within a month, 31 cases were located and these patients underwent ophthalmic and peripheral nerve assessment and completed lifestyle questionnaires.

Results: Five of the 31 individuals were found to have bilateral symmetrical optic neuropathy. Although it was not possible to fully ascertain etiology, the phenotype is compatible with epidemic, presumed nutritional, optic neuropathy described in Tanzania. Comparative prevalence data suggest a prevalence of 0.07% in The Gambia based on a total sample size of 6873 vs 2.4% in Tanzania.

Conclusion: Our data indicate that bilateral optic neuropathy is nonepidemic in The Gambia. Rare vitamin B₁₂ and folate deficiencies reported in rural Gambians may explain the low prevalence because previous epidemics were due to nutrient deficiency. Our study is the only available estimate of epidemic optic neuropathy in The Gambia and, as such, provides an important contribution to our knowledge in identifying characteristics that may cause specific populations to be more susceptible to this public health burden.

Strachan (1) was among the first to extensively record an optic neuropathy epidemic in the West Indies toward the end of the 19th century. Hundreds of patients were documented with dimness of vision and painful “burning” sensations of the lower limbs, a clinical entity that was later named Strachan syndrome and linked to nutritional deficiency in prisoners of war during World War II (2).

In Africa, over the past 80 years, there are reports of outbreaks of Tropical Ataxic Neuropathy (TAN) in Nigeria (3), and a form of acute paralysis known as “Konzo” in Democratic Republic of Congo (formerly Zaire) (4), Mozambique (5), and Tanzania (6). First reported in 1988, the most recent epidemic, also occurred in Tanzania, appeared to be endemic within the secondary school population of Dar es Salaam (7). Patients presented with bilateral, simultaneous, usually painless, visual loss over 2–12 weeks and were found to have impaired color vision, central or cecocentral scotomas, and, in many cases, peripheral neuropathy (8–10). This epidemic was distinct from TAN and Konzo but resembled Cuban Epidemic Optic Neuropathy (11). Low levels of dietary B-vitamin were thought to be responsible for the Cuban epidemic, and widespread B-vitamin supplementation largely resolved the outbreak (11). Likewise, a similar etiology is suspected in Tanzania. Preliminary biochemical analyses indicate B-vitamin deficiencies, although a similar deficiency was seen in healthy controls (A.A. Dalmar, MD, PhD, personal communication, 2012). Therefore, a multifactorial etiology has been proposed, including nutritional, genetic, and environmental factors. Such a hypothesis is supported by the most recent data from Tanzania, in which folate status and indoor smoke pollution were identified as risk factors (12).

Interest in epidemic optic neuropathy, especially in Africa, has been largely reignited by these Tanzanian cases. A study has confirmed that the condition may also be at epidemic levels in Somalia (13).

Previous reports in Africa have focused on eastern and central African countries, with little data from the western area of the continent. Our goal was to measure the prevalence...
of optic neuropathy in The Gambia as part of a 1996 national survey on the impact of a national eye care program on blindness and low vision prevalence. In addition, comparisons with a parallel prevalence study in the Tanzanian epidemic were undertaken.

METHODS

The Gambia

In 1996, the National Blindness Survey was conducted in The Gambia, a West African country. The sample population was selected using multistage random sampling. The country was stratified into 7 health regions, and districts from each region were randomly selected using proportional probability sampling (PPS). Settlements were selected from each district, also using PPS, with stratification by settlement size (small <400 residents and large ≥400 residents). A compound-to-compound census was then undertaken to provide a current sampling frame for subsequent compound selection. All residents in a compound were examined, resulting in a sample size of 6873 individuals (14).

A 2-part ophthalmic examination was carried out:

Part 1: Visual acuity was measured in all subjects aged 5 years and older, and the anterior segment was examined with a focused light and ×2 loupe. All those who were 35 years and older, and any younger person with a visual acuity of G/18 (20/60) or less in either eye, were referred for detailed examination by an experienced ophthalmologist. Visual fields were screened (Henson CFA3000 visual field analyser; Henson Instruments, Redditch, UK), intraocular pressure was measured (Schiotz tonometer; Akriti, Hyderabad, India), and the optic disc was inspected. Thirty-three cases of low vision or blindness in which optic neuropathy was a sole cause of visual loss were identified during the initial study.

Part 2: Within 1 month, investigators returned and invited each patient with optic neuropathy to a local clinic to undergo additional testing.

1. Visual acuity (Snellen chart) and color vision (Ishihara plates).
2. Visual fields (Henson field analyser) and tangent screen color fields using a red target (laser pointer).
3. Peripheral nerve function (knee and ankle jerk reflexes: temperature, pain, touch, and joint position sensation; movement coordination).
5. Standard ophthalmic examination.

Tanzania

A parallel prevalence survey in Tanzania was also conducted (15). Stratified systematic sampling was used to select a sample of 1078 people, based on stratification of the 21 residential areas of Dar es Salaam. The study was powered to obtain statistically significant confidence intervals, accounting for study design and assumed prevalence rate. Clinical examination included assessment of visual acuity (Snellen chart), color vision (Ishihara plates), and fundus examination using direct ophthalmoscopy.

The Gambia and Tanzanian patients were asked about their clinical history and lifestyle. The case definition for bilateral optic neuropathy used in each study is identical to that used in previous studies: bilateral simultaneous visual loss over at least 3 days (the interocular differences in visual acuity being no greater than 2 lines on the Snellen chart) impaired color vision, bilateral central or cecocentral scotomas at onset, and temporal pallor of the optic discs (8).

Data Handling

Estimates of prevalence and 95% confidence interval were calculated using SPSS software (IBM Software, Portsmouth, UK), adjusting for excess sampling error (extrabinomial variation) arising from the study design.

Ethics

Ethical approval was provided by the Gambia Government/Medical Research Council Joint Ethics Committee.

RESULTS

A high response rate was achieved. Thirty-one of 33 (93.9%) individuals initially identified as having optic neuropathy in the 1996 Gambia National Blindness Survey were traced and examined. From these, 5 cases were identified as bilateral (presumed nutritional) optic neuropathy. Of those presenting with bilateral optic neuropathy, the mean age was 42 (±7.5) years and 3 of the 5 cases were women. All patients displayed temporal pallor of the optic discs and some level of color vision impairment (unable to read at least 1 Ishihara plate). On ophthalmoscopy, abnormalities of the nerve fiber layer were detected in all cases, particularly involving the papillomacular bundle (Fig. 1). All individuals had been suffering from optic neuropathy for over 2 years and some more than 2 years, at the time of the survey. None used alcohol, and 2 were current smokers. At time of symptom onset, 4 of the 5 patients admitted to cassava consumption ranging from daily to once per week consumption. No other dietary factors or medicinal uses were identified. Table 1 summarizes the additional characteristics of the patients with optic neuropathy. All patients lived in rural areas of The Gambia, and 3 reported receiving previous treatment with eye drops, although it was not possible to determine the composition of the drops. No treatment involved vitamin supplements, and only 1 patient reported any improvement in symptoms. Based on the survey totaling 6873 persons, the overall prevalence of bilateral optic neuropathy in The Gambia was 0.07%.
DISCUSSION

A clinical review of bilateral optic neuropathy cases from the 1996 National Blindness Survey in The Gambia identified 5 individuals likely to be suffering from the clinical entity seen in Tanzania termed "epidemic optic neuropathy." No lifestyle factors were common to the cases other than cassava consumption at the time of symptom onset in 4 of 5 cases. Given its widespread use in West Africa, cassava is unlikely to have been a specific risk factor for Gambian bilateral optic neuropathy. This would be consistent with findings from Tanzania (16), although the absence of a control group makes it difficult to draw definitive conclusions. The chronic nature of the cases also limits our knowledge of exposures at the time of optic neuropathy onset, and the long duration between the onset of disease clinical evaluation makes recall bias and lifestyle changes probable. In addition, the duration of bilateral optic neuropathy in our patients could not be accurately determined.

We set out to provide prevalence data on Gambian bilateral optic neuropathy to assess any potential undetected burden on the country. Bilateral optic neuropathy in Dar es Salaam, Tanzania, was 34 times higher than in The Gambia in 1996 (Table 2). This indicates that the cases of bilateral optic neuropathy were nonepidemic in The Gambia. However, there were limitations in our study. Although identical case definitions were used in comparing the populations of The Gambia and Tanzania, our ability to standardize methodologies was limited given that The Gambian study was conducted within a larger national survey. Yet, if any cases were excluded, this should have occurred synonymously in each study given that identical case criteria were used. Differences in the age distribution of the 2 populations may account for some of the difference in the prevalent rates. Also, while The Gambian survey was conducted on a countrywide level, the survey in Tanzania included only the city of Dar es Salaam. Finally, we did not exclude other potential causes of bilateral optic neuropathy, such as Leber hereditary optic neuropathy and neuromyelitis optica.

Our results provide for the first time a prevalence estimate of optic neuropathy in a coastal West African country. Data on B-vitamin status indicate rare deficiencies in vitamin B_{12} and folate in the rural Gambian population.

**TABLE 1.** Characteristics of cases from The Gambia presenting with bilateral optic neuropathy

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
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<td>Visual acuity*</td>
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</tr>
<tr>
<td>&lt;3/60</td>
<td>1</td>
</tr>
<tr>
<td>Severely impaired color vision†</td>
<td>3</td>
</tr>
<tr>
<td>Abnormalities of retinal nerve fiber layer</td>
<td>5</td>
</tr>
<tr>
<td>Numbness/burning of lower limbs</td>
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<tr>
<td>Reported weight loss at symptom onset</td>
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<tr>
<td>Breast-feeding (of the 3 women)</td>
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<tr>
<td>Consuming meat at least once per week</td>
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<td>Memory loss</td>
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†Able to read a maximum of 4 of 15 Ishihara plates.

**TABLE 2.** Prevalence comparison of bilateral optic neuropathy in The Gambia and Tanzania

<table>
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<th>Country</th>
<th>n</th>
<th>Prevalence (%)</th>
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</tr>
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<td>Tanzania</td>
<td>1078</td>
<td>2.4</td>
<td>1.7–3.0</td>
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CI, confidence interval.
at the time of the survey (17), which may, at least in part, explain the low prevalence of bilateral optic neuropathy, in The Gambia compared with Tanzania. (10,12,18,19).

ACKNOWLEDGMENTS

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A Case of Isolated Susac Occlusive Retinal Vasculitis

Mark E. Seamone, MS, Michael Fielden, MD, FRCSC

Abstract: Susac syndrome is characterized by encephalopathy, sensorineural hearing loss, and branch retinal artery occlusion. Additional ocular findings include arteriolar wall hyperfluorescence and Gass plaques. We present a 51-year-old Caucasian woman with ophthalmologic findings indicative of Susac syndrome in the setting of tinnitus and migraine with aura.

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The authors report no conflicts of interest.

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A 51-year-old Caucasian woman was referred for retinal vascular sheathing in the right eye with spotty visual field loss and dysphotopsia bilaterally. Review of systems was significant for tinnitus and migraine with aura. Visual acuity...
was 20/20 in the right eye and 20/15 in the left eye. Left fundus examination revealed an inferonasal branch retinal artery occlusion (BRAO) with arteriolar sheathing in both eyes. Fluorescein angiography confirmed BRAO in the left eye and demonstrated arteriolar wall hyperfluorescence (AWH) along the right superotemporal arteriole (Fig. 1). Interestingly, BRAO and AWH occurred at independent locations.

An extensive systemic workup failed to reveal an autoimmune or infectious cause of retinal vasculopathy. Given the clinical findings associated with migraine aura and tinnitus, Susac syndrome was considered a potential diagnosis. The patient was placed on a dose of 30 mg of prednisone daily. Three weeks later, visual acuity was stable. Brain magnetic resonance imaging was normal without evidence of corpus callosum microinfarctions. Audiography was also normal. Neurology consultation showed no evidence of encephalopathy.

Two weeks later, the patient reported decreased vision in the right eye. She was found to have a BRAO along the right superotemporal arteriolar arcade with the presence of Gass plaques (GPs) (Fig. 2). The location of this BRAO did not correlate with the location of AWH observed on the initial presentation. The patient’s prednisone dose was increased to 50 mg daily and then tapered as methotrexate was begun. The patient remains stable on 25 mg of methotrexate and 5 mg of folic acid, both taken weekly. There has been no recurrence of retinal vasculitis over 14 months of follow-up.

Susac syndrome is a rare neurologic disorder characterized by encephalopathy, sensorineural hearing loss, and BRAO (1). It has been divided into 2 subtypes: 1) encephalopathic with changes in affect and neuroimaging findings of corpus callosum infarcts and 2) retinal vasculitis with BRAO (2). The BRAO subtype is characterized by retinal vasculitis and minimal or absent neurologic involvement. Cochleovestibular involvement may manifest as tinnitus or vertigo (2). The ophthalmologic findings of Susac syndrome include recurrent BRAO, AWH, and GP (3,4). These plaques, thought to be atheromatous in nature, develop in areas of acute arteriolar wall injury. Typically, GP are yellow, may be refractile or nonrefractile, and, in contrast to Hollenhorst plaques, usually are located away from arteriolar bifurcations (3,4).

The diagnosis of Susac syndrome often is not considered in the absence of the complete clinical triad. In our patient, the observation of BRAO, GP, and AWH in the setting of tinnitus and migraine is consistent with Susac syndrome. The dissociation between the presence of AWH and BRAO, as seen in our case, is a hallmark of Susac syndrome and lends further support to the diagnosis. We propose 2 explanations regarding the absence of corpus callosum involvement and changes in affect. First, retinal vasculitis may have been the initial disease presentation and progression to fulminant Susac syndrome was halted by the initiation of immunosuppressive
agents. Second, this may represent a rare case of BRAO subtype of Susac syndrome.

REFERENCES

Partial Third Nerve Palsy and Ocular Neuromyotonia From Displacement of Posterior Communicating Artery Detected by High-Resolution MRI

Franz Marie Cruz, MD, Ari M. Blitz, MD, Prem S. Subramanian, MD, PhD

Abstract: Ocular neuromyotonia is an unusual condition in which sustained, undesired contraction of one or more extraocular muscles occurs after normal muscle activation. Although most commonly reported after parasellar cranial irradiation for tumor, chronic nonaneurysmal vascular compression of the third nerve can produce partial ocular motor nerve paresis and ocular neuromyotonia. A 75-year-old woman presented with intermittent left-gaze-evoked binocular diplopia. She had an incomplete right third nerve palsy but became symptomatically diplopic and esotropic upon sustained left gaze. High-resolution brain magnetic resonance imaging showed displacement of the right posterior communicating artery and contact with the right third nerve. Gaze-evoked diplopia resolved with carbamazepine, but a partial third nerve paresis remained.

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The patient was diagnosed with a partial right pupil-involving third nerve palsy and ocular neuromyotonia. MRI with attention to the third nerve revealed displacement of the right posterior communicating artery and contact with the cisternal segment of the right third nerve (Fig. 3A, B). The patient was prescribed carbamazepine, 200 mg twice daily, with complete resolution of ocular neuromyotonia. The partial third nerve palsy was unchanged. When the patient stopped carbamazepine 3 months later, the ocular neuromyotonia returned; it resolved again 2 days after carbamazepine was resumed.

Ocular neuromyotonia is an acquired disorder characterized by paroxysmal neuronal discharges resulting in brief continuous contractions of extraocular muscles. It is a rare cause of episodic binocular diplopia. It most commonly involves the third nerve, followed by the fourth and sixth nerves (1) and may occur in a setting of chronic ocular motor nerve cranial nerve palsy (2). Lid and pupil synkineses with third nerve involvement may occur (1,2). Ocular neuromyotonia may occur spontaneously (3) or following prolonged gaze in the direction of action of the involved extraocular muscle (2,3). It also has been reported following alcohol consumption (2). It is a delayed consequence of cranial irradiation, particularly to the parasellar region. Less common causes include Graves dysthyroid orbitopathy (4), cavernous sinus disease (5,6), and neurovascular compression by an arterial aneurysm (2,7) or a dolichoectatic basilar artery (8). On occasion, no specific cause is identified (3). To our knowledge, ocular neuromyotonia and partial pupil-involving third nerve paresis resulting from displacement of the posterior communicating artery and contact with the third nerve have not been reported.

Evaluation of patients with ocular neuromyotonia requires neuroimaging (2,9). If a structural abnormality is not identified with conventional brain MRI techniques, one should consider additional MRI sequences, including fast-imaging employing steady-state acquisition (FIESTA), constructive interference in the steady-state (CISS), and volumetric interpolated breath-hold examination (VIBE). FIESTA and CISS provide high spatial resolution sequences capable of depicting the entire course of the cranial nerves including segments that are not visible using traditional techniques (10). Inoue et al (11) used FIESTA in a patient with ocular neuromyotonia to identify vascular compression of the third nerve at its root exit zone. The patient had no evidence of third nerve palsy. VIBE was designed to shorten acquisition time, enhance image contrast, and decrease image artifact. Its application includes imaging of the lungs, liver, and brain (12).

FIG. 2. Following sustained left gaze, the patient develops an esotropia and deficits in elevation (A), and depression (B, C) of the right eye.

FIG. 3. High-resolution magnetic resonance imaging of the brain with attention to the skull base. A. On precontrast coronal constructive interference in the steady state images, the right posterior communicating artery (long arrow) contacts the right cisternal third nerve (short arrow). The left posterior communicating artery (dashed long arrow) does not contact the third nerve (arrowhead). B. On postcontrast axial volumetric interpolated breath-hold examination images, the right cisternal third nerve (short arrow) is seen adjacent to the right posterior communicating artery (long arrow) and demonstrates enhancement when compared with the left third nerve (arrowhead).
Possible pathophysiologic mechanisms of ocular neuromyotonia include unstable motor nerve membranes, ephaptic transmission across adjacent nerves, and abnormal extracellular potassium concentration (2,3). We believe that ephaptic transmission rather than aberrant regeneration of the third nerve is the mechanism for the progressive eyelid elevation during sustained down gaze seen in our patient. This is also supported by our patient’s excellent response to treatment with carbamazepine, a membrane-stabilizing agent.

REFERENCES
Bilateral Optic Neuritis due to Malaria

Joseph G. Chacko, MD, Sanjeeva Onteddu, MD, Eric R. Rosenbaum, MD, MPH

Abstract: Malaria is a mosquito-borne infectious disease caused by protists of the genus *Plasmodium*. Malaria is widespread in tropical regions around the equator, including much of sub-Saharan Africa, Asia, and the Americas, and uncommonly seen in the developed world. Although a variety of ocular manifestations have been linked to malaria, optic neuritis is rare. We report a patient who developed bilateral optic neuritis after he was treated successfully for acute falciparum malaria.

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A 40-year-old African man, who had been living in the United States for 12 years, traveled home to Zimbabwe. Before leaving, he did not take malaria prophylaxis. He returned to the United States after his 2-week trip and became ill with headache, fever, chills, and sweats. A blood smear was positive for malarial parasites, the Centers for Disease Control was contacted, and the patient was started on quinine and transferred to our hospital for further care.

On arrival, he appeared well-nourished but was febrile, diaphoretic, and icteric. His vital signs were as follows: temperature 103.7°F, pulse 127 beats per minute, respiration 20/min, and blood pressure 146/71 mm Hg. Systemic and neurologic examinations were otherwise normal. His white blood cell count was of 5870 cells/ml (normal, 3000–12,000 cells/ml), hemoglobin 12.2 g/dL (normal, 13.5–17.5 g/dL), and total bilirubin of 6.0 mg/dL (normal, 0.2–1.2 mg/dL). Peripheral blood smear was positive for *Plasmodium falciparum* (Fig. 1). The patient received 3 days of oral quinine (650 mg every 6 hours) and doxycycline (100 mg twice a day), followed by a 3-day course of artemether/lumefantrine. His repeat blood smear showed no malarial parasites, and he became less icteric and was discharged home.

One month later, the patient presented with bilaterally decreased vision. He reported gradually worsening vision in the left eye after discharge, followed 1 week later with involvement of the right eye. He also described pain with eye movement. On examination, visual acuity was count fingers at 1 foot, right eye, and 20/400, left eye. Pupils were 7 mm and sluggishly reactive to light without a relative afferent pupillary defect. Eye movements were full. Slit-lamp examination was significant for...
1+ cell in the right anterior chamber and rare cell in the left eye. Goldmann visual field testing revealed bilateral cecocentral scotomas. There was a mild bilateral optic disc edema (Fig. 2), and the retinal examination was normal.

Magnetic resonance imaging showed bilateral enhancement of the orbital portions of the optic nerves (Fig. 3). Repeat peripheral blood smear did not reveal any malarial parasites, and cerebrospinal fluid analysis was normal. The patient was started on intravenous solumedrol 250 mg every 6 hours for 3 days followed by oral prednisone taper over 4 weeks. Two months later, visual acuity was 20/20 in each eye with resolution of the cecocentral scotomas and optic disc edema.

The ocular manifestations of malaria have been described previously, and retinal abnormalities predominate, particularly in the setting of anemia (1–4). Optic atrophy may be the result of chronic papilledema, ischemic optic neuropathy, or optic neuritis. Flower et al (1) reported the association with ischemic optic neuropathy in a 56-year-old man with malaria caused by *Plasmodium vivax* who experienced vision loss in his left eye with a pale, swollen optic disc, peripapillary hemorrhage, and a macular star.

Previous reports have documented malaria-associated optic neuritis in the context of active infection, possibly because of tissue hypoxia related to hemolysis, sluggish blood flow, and increased capillary permeability. Wadia (2) reported the first 2 cases of malaria-associated retrobulbar optic neuritis in 1990. Both patients, a 28-year-old man and a 31-year-old woman, developed visual loss concurrently with their systemic malarial symptoms. Both were treated with intravenous quinine and retrobulbar injections of dexamethasone and each attained full visual recovery. Kale et al (3) reported a 24-year-old woman with *P. falciparum* who developed bilateral light perception vision with poorly reactive pupils and normal fundi 1 day after beginning intravenous quinine therapy. She was switched to artether and given intravenous methylprednisolone for 3 days, followed by oral steroid taper for 6 weeks. Vision improved to 20/60 in each eye over the ensuing 2 months.

Our case is unique in that bilateral visual loss occurred approximately 1 month after onset of systemic symptoms. The patient's blood smear after treatment and before discharge from the hospital did not show any malarial parasites. The timing of visual loss in our patient, the concomitant mild iritis, and improved vision with steroid therapy supports a postinfection, immune-related mechanism.

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Restricted Diffusion of the Superior and Inferior Ophthalmic Veins in Cavernous Sinus Thrombosis

Lindsey B. De Lott, MD, Jonathan D. Trobe, MD, Hemant Parmar, MD

Abstract: Two previous reports have described restricted diffusion in thrombosed superior ophthalmic veins (SOVs) in patients with cavernous sinus thrombosis (CST). We report a patient who displayed restricted diffusion in both the SOV and inferior ophthalmic vein in CST consequent to a masticator space abscess. The orbital vascular imaging findings added support to the cavernous sinus findings in making the diagnosis of CST. Diffusion-weighted imaging of the orbit is a valuable asset in this setting.

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A 59-year-old man presented to the emergency room with several weeks of pain in the left jaw exacerbated by chewing and talking. Four days earlier, he had noticed progressive swelling of the left cheek and neck followed by a persistent severe frontal headache.

Temperature was 39.1°C, heart rate was 111 beats per minute, and blood pressure was 106/52 mm Hg. There was a marked left facial swelling without erythema. Purulent fluid could be expressed from the gingiva upon palpation of the left cheek, suggesting an abscess.

The leukocyte count was 34.3 K/mm$^3$ with 86% neutrophils. The platelet count was 417 K/mm$^3$. Necrotic computed tomography (CT) showed extensive dental and periodontal disease with multiple abscesses in the left masticator space involving the left masseter and lateral and medial pterygoid muscles (Fig. 1A).

Incision and drainage of the abscesses was performed. Vancomycin, clindamycin, and levofloxacin were instituted.

The following day he reported reduced vision in the right eye and double vision on left gaze and when reading. Ophthalmologic examination revealed a best-corrected visual acuity of 20/60 in the right eye and 20/20 in the left eye. Pupils constricted normally without an afferent pupillary defect. There were no abnormalities of the left eye.

There were 3 mm of right upper eyelid ptosis with upper and lower eyelid edema and 3 mm of right eye proptosis as

FIG. 1. Computed tomography (CT). A. Axial contrast-enhanced neck CT shows multiple abscesses in the left masticator space involving the left masseter and medial pterygoids (arrows). B. A more rostral image shows lateral bulging of both cavernous sinuses (arrows). There is enhancement of the intracavernous carotid arteries as well as the superior sagittal sinus (arrowhead), but none of the cavernous sinuses, suggestive of thrombosis.
FIG. 2. Magnetic resonance imaging (MRI). A. Contrast-enhanced axial T1 MRI of the orbits with fat suppression shows enhancement in the right orbital fat, optic nerve sheath, and extraocular muscles. B. Contrast axial T1 scan shows bulging of the lateral walls of the cavernous sinuses (arrows) and inhomogeneous enhancement of each sinus. C. Contrast coronal T1 images with fat suppression reveal enhancement of the right orbital fat and optic nerve sheath. The right superior (SOV) and inferior ophthalmic veins (IOV) fail to opacify (arrows), compared with normal filling of these veins in the left orbit (arrowheads). Diffusion-weighted imaging (DWI) shows increased signal in the right IOV (D) and right SOV (E, F). G, H, I. Restricted diffusion is confirmed on corresponding ADC maps.
measured with the Hertel exophthalmometer. The right eye was tender to palpation. Its conjunctiva was hyperemic and edematous. Abduction was 50% of normal, and supraduction, infraduction, and adduction were 25% of normal. Intraocular pressures were 15 mm Hg in the right eye and 9 mm Hg in the left eye. Ophthalmoscopy was normal. Neurologic examination was normal.

As the ophthalmic findings suggested the possibility of a cavernous sinus lesion, the neck CT was rereviewed with more attention to the cavernous sinus. The CT study was performed using a split-bolus technique (50 mL of contrast bolus followed by a 75 mL of contrast bolus 90 seconds later) according to our standard protocol, as some neck tumors demonstrate late contrast enhancement. Both arterial and venous phases were captured. There was nonopacification and lateral bulging of both cavernous sinuses (Fig. 1B). A dedicated contrast-enhanced orbital CT was also performed and did not reveal an intraorbital abscess.

Magnetic resonance imaging (MRI) of the brain and orbits showed diffuse enhancement of the right orbital fat, optic nerve sheath, and extraocular muscles (Fig. 2A). There was bulging and excessive enhancement of the lateral dural wall of the cavernous sinuses, as well as inhomogeneous enhancement of the sinuses, suggestive of thrombosis (Fig. 2B). Coronal images at the midorbital level showed nonopacification of the right superior ophthalmic vein (SOV) and inferior ophthalmic vein (IOV) (Fig. 2C). Diffusion-weighted imaging (DWI) showed increased signal (restricted diffusion) within the right IOV (Fig. 2D, G) and SOV, suggestive of thrombosis (Fig. 2E, F, H, I). These imaging findings were considered sufficiently conclusive for cavernous sinus thrombosis (CST) such that venography was not performed.

Treatment with intravenous heparin was initiated. Blood cultures and material from the abscesses grew Streptococcus anginosus, a facultative oral anaerobe capable of producing systemic infections. Antibiotics were changed to ceftriaxone and metronidazole to treat infection by Streptococcus and other oral anaerobes.

Within 48 hours, the facial and periorbital swelling markedly subsided. Within 1 week, visual acuity and ocular motility had returned to normal. After 6 weeks, antibiotics and anticoagulation were discontinued.

**DISCUSSION**

Restricted diffusion within a thrombosed SOV in CST was first reported in this journal in a case of pansinusitis (1). A subsequent publication documented restricted diffusion in the SOVs bilaterally in a 64-year-old woman with a dental abscess (2). This is the first report of CST with MRI evidence of restricted diffusion, not only in a thrombosed SOV but also in a thrombosed IOV.

By demonstrating restricted diffusion in the SOV and IOV, DWI confirmed thrombosis of these veins and the diagnosis of CST suggested by other neuroimaging features. These features include nonopacification and lateral wall bulging of both cavernous sinuses during the venous phase of the neck CT, excessive enhancement of the dural wall of the cavernous sinuses and inhomogenous contrast opacification of both sinuses and the right SOV and IOV on contrast-enhanced MRI.

The high DWI signal in thrombosed vessels in the hyperacute stage likely results from multiple mechanisms including clot retraction, plasma resorption, osmotic changes in the extravascular environment, and changes in the hemoglobin molecule (3). As the thrombus ages and hemoglobin molecule changes, the signal becomes hypointense. The exception is the late subacute phase, in which red cell lysis and inflammatory cell infiltration may cause the DWI signal to become high again (3,4).

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Congenital Mydriasis Associated With Megacystis Microcolon Intestinal Hypoperistalsis Syndrome

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Abstract: We report a case of congenital mydriasis in a neonate with megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS). Pilocarpine testing and gastrointestinal pathology in our patient suggest that the mydriasis is due to an underlying smooth muscle myopathy of the iris sphincter muscle. These findings may have important implications regarding the pathogenesis of MMIHS.


Megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS) is a rare congenital disease affecting smooth muscle peristalsis in the gastrointestinal (GI) tract and urinary bladder. Although the literature is full of hypotheses regarding the etiology of MMIHS, there is still no established pathophysiology. A mouse model lacking the α3 subunit of the nicotinic acetylcholine receptor (nAChR) has demonstrated phenotypic features of MMIHS, including megacystis, distended bowel, postnatal growth deficiency, and death within the first week of life (1). The mouse model also exhibited marked pupillary mydriasis, but at the time, mydriasis had not been reported in humans with MMIHS. A report of an infant with MMIHS and bilateral mydriasis further supports the theory that MMIHS is caused by a genetic defect in the nAChR α3 subunit (2). We report the second case of bilateral mydriasis associated with MMIHS and present the results of pilocarpine testing that, along with the histopathology of the excised intestine, suggest an underlying smooth muscle myopathy in MMIHS.

CASE REPORT

A 23-year-old otherwise healthy Caucasian woman with no family history of consanguinity presented to our institution after an abnormal routine fetal ultrasound during an uncomplicated second pregnancy. Her first pregnancy was complicated by mild pre-eclampsia but resulted in a healthy baby boy. A high-resolution ultrasound at 28 weeks of gestational age showed a female fetus at the 95th percentile weight for her age and a markedly distended urinary bladder. Fetal magnetic resonance imaging (MRI) (Fig. 1) confirmed the ultrasound findings and also demonstrated a small sigmoid and descending colon raising suspicion for MMIHS.

The child was born at 35 weeks gestational age through elective cesarean section and appeared neurologically normal except for mydriatic pupils bilaterally. She failed to tolerate any feeds, necessitating parenteral nutrition through a central venous line. Prenatal and postnatal testing for infectious teratogens, including toxoplasmosis, rubella, cytomegalovirus, and herpes (TORCH infections), were negative. At 8 weeks of age, it was recommended that she undergo extensive abdominal surgery. At operation, she was found to have intestinal malrotation with midgut volvulus (presumably having occurred in utero), multiple small intestinal atresias, and a microcolon. Several atresias were repaired, and nonviable intestine was resected (Fig. 2A), leaving approximately 65 cm of small bowel, an intact ileocecal valve, and a complete colon. A gastrostomy tube was placed. Postoperatively, feeding attempts remained unsuccessful. A second
FIG. 1. Sagittal T1 magnetic resonance imaging shows a massively enlarged fetal bladder (straight arrow) compared with the normal maternal bladder (arrowhead).

laparotomy was required 6 weeks after the first and revealed extensive adhesions and an intra-abdominal abscess. She has since remained dependent on parenteral nutrition and is being considered for bowel transplantation.

Pathology of the resected small intestine (Fig. 2B, C) showed the circular layer of the muscularis propria to be markedly thicker than the focally discontinuous longitudinal layer of the muscularis propria. No aganglionic segments were seen, and the number of ganglion cells appeared normal (Fig. 2D). Trichrome stains showed increased fibrous tissue in the submucosa and longitudinal layer of muscularis propria (Fig. 2E). Desmin and smooth muscle actin stains highlighted thinning and discontinuity of the longitudinal layer of the muscularis propria. A c-Kit stain demonstrated the presence of interstitial cells of Cajal.

Neuro-ophthalmic evaluation at 3.5 months of age demonstrated intermittent fixation and following of a toy with both eyes. Motility appeared full with normal alignment on Hirschberg testing. There was no nystagmus. Facial grimacing was normal and symmetric. Corneal sensation was normal with cotton swab testing. Portable slit-lamp examination did not show cataract formation or iris transillumination but was remarkable for bilateral 7-mm nonreactive pupils with diffusely hypotrophic appearing irides with diminished surface crypts. There were spoke-like remnants of iris vessels spanning from the iris collarette across a hypotrophic pupillary ruff to the anterior lens surface. Fundus examination was normal in both eyes.

One week later, pupillary testing was performed by placing 2 sets of 0.125% pilocarpine drops 5 minutes apart in both eyes. After 30 minutes, there was no significant change between the pre-drop (Fig. 3A) and the post-drop pupillary appearance (Fig. 3B). Next, an additional 2 sets of 1% pilocarpine drops were placed 5 minutes apart in both eyes. After 30 minutes, there was again no significant change in the pupillary examination (Fig. 3C). MRI of the brain and orbits was unremarkable, and an electroencephalogram (EEG) revealed no epileptiform activity.

DISCUSSION

MMIHS classically presents at birth in female infants (M:F = 1:2.3), with abdominal distension, an enlarged nonobstructed bladder, and a microcolon related to GI hypoperistalsis (3–5). The majority of MMIHS patients fail enteral feeds and succumb to complications of chronic parenteral nutrition in the first year of life (3,6). GI promotility medications (3) and numerous surgical interventions (2,3,5–7) often fail due to severe GI hypoperistalsis. A review of GI histopathology in MMIHS found that 72 of 93 cases showed a normal quantity and morphology of ganglion cells in excised intestinal segments (3). As in our case, the intestinal longitudinal muscle layer typically shows thinning and fibrosis on light microscopy (8), whereas electron microscopy has disclosed myopathic changes including vacuolar degeneration of smooth muscle cells (8–11). Not observed in our case, excised bowel in MMIHS may show deficient immunohistochemical staining for α-smooth muscle actin (10,12).

Numerous hypotheses for the pathogenesis of MMIHS have been proposed, including inflammatory (13), drug-induced teratogenesis (14), hormonal (15), neurogenic (1,2,16,17), and myogenic (8,10,12,18) causes. Over time, 2 leading theories for the pathogenesis of MMIHS have emerged: a smooth muscle myopathy related to abnormal expression of smooth muscle actin and a neurogenic disturbance caused by a mutation in the α3 subunit of the nAChR in parasympathetic ganglia.

Anatomical studies of chickens and guinea pigs have found that the α3 subunit of the nAChR to be prevalent in autonomic ganglia (19,20), and humans with antibodies to the α3 subunit of the nAChR demonstrate widespread autonomic dysfunction correlating with antibody levels (21). Xu et al (1) reported a mouse model lacking the α3 subunit of the nAChR that shares some similarities with human MMIHS, including megacystis, distended bowel, postnatal growth deficiency, and premature death leading to the theory that MMIHS is caused by an α3 nAChR subunit mutation. Subsequent in situ hybridization studies have shown decreased expression of the nAChR α3 subunit in MMIHS intestinal specimens (16). Other features of the nAChR α3 subunit knockout murine model including bilateral pupillary mydriasis were not associated with MMIHS until a report described pupillary mydriasis in association with MMIHS (2).

We considered a variety of causes of neonatal pupillary dilation in our patient (Table 1). She received no sympathomimetic medications or eye drops. The iris was hypotrophic,
but structurally complete, making aniridia unlikely. Normal alignment, full motility, and an absence of ptosis excluded bilateral third nerve palsies. A normal EEG and MRI, lack of fluctuation in pupil size, and absence of seizure-like activity excluded seizure-associated mydriasis. Although congenital, bilateral tonic pupils can occur and have been reported in association with neuroblastoma (22), congenital tonic pupils should exhibit supersensitivity to dilute pilocarpine (0.1%) drops.

After a lack of pupillary response to 1% pilocarpine and a careful evaluation failed to reveal an alternative explanation, the diagnosis of congenital mydriasis (CM) associated with MMIHS was made. CM is defined as congenital pupillary dilation (>6 mm in diameter), grossly normal iris structure, and diminished accommodation in some cases (23,24). The pathophysiology underlying iris dysgenesis in CM remains unclear and likely reflects many different etiologies. A high frequency of hypotrophic irides and persistent pupillary membranes are observed in CM cases (23,25–28). Other systemic diseases associated with CM include Waardenburg syndrome, isolated patent ductus arteriosus (25,26,28–30), and the recently described multisystemic smooth muscle dysfunction syndrome (MSMDS) (31,32). MSMDS is a systemic disorder of smooth muscle function affecting vascular, GI, genitourinary, pulmonary, and iris smooth muscle that has been associated with mutations of the smooth muscle-specific contractile protein alpha actin (ACTA2) (31,32). Although similarities exist between MMIHS and MSMDS, many features of MSMDS, such as thoracic aortic aneurysms, periventricular white matter changes on MRI, and central nervous system moyamoya-like vascular abnormalities, are not characteristic of MMIHS and were not seen in our patient (31).

Our patient’s lack of pupillary constriction to 1% pilocarpine suggests that CM in MMIHS is caused by a structural

**FIG. 2.** A. Resected maldeveloped small intestine demonstrates areas of atresia (arrow). B. Segment of resected intestine reveals circular layer (CL) of the muscularis propria to be markedly thicker than the longitudinal layer (LL) of the muscularis propria (hematoxylin and eosin, ×100). C. There is focal discontinuity (between arrows) within the LL of the muscularis propria (hematoxylin and eosin, ×100). D. There are normal quantity and morphology of ganglion cells (arrows) within the resected intestine (hematoxylin and eosin, ×200). E. Increased blue staining of fibrous tissue is present in the LL of the muscularis propria (trichrome, ×40).
iris abnormality such as a smooth muscle myopathy, although the possibility exists that the myopathic and neurogenic theories for MMIHS may not be mutually exclusive. Graf and Jungherr (26) theorized that CM could arise from “orthograde transsynaptic dysgenesis” of the iris musculature due to a “lack of sensibility of the cholinergic receptors.” In accord with this theory, a genetic mutation causing dysfunction of the nAChR α3 subunit in both sympathetic and parasympathetic ganglia could lead to a secondary myopathy of smooth muscle throughout the GI tract, bladder, and, rarely, the iris smooth muscle structures as exhibited in the α3 nAChR knockout mouse model (1). Further discussion is available (see Supplemental Digital Content, http://links.lww.com/WNO/A67).

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Posterior Reversible Encephalopathy Syndrome in a Leber Hereditary Optic Neuropathy Patient With Mitochondrial DNA 11778G>A Point Mutation

Yuwei Da, MD, Xuxiang Zhang, MD, Fang Li, MD, Xiaoping Yang, MD, Xinqing Zhang, MD, Jianping Jia, MD

Abstract: Leber hereditary optic neuropathy (LHON) is a maternally inherited mitochondrial disorder that primarily affects the optic nerve. We report a case of reduced visual acuity secondary to optic atrophy in a 13-year-old boy. Transient seizures developed subsequently. Serial magnetic resonance imaging of the brain showed posterior reversible encephalopathy syndrome. Ragged red fibers were not detected on skeletal muscle biopsy. A 11778G>A mitochondrial DNA point mutation was identified in the lymphocytes isolated from peripheral blood. His younger brother was a carrier with the same mutation. The presentation of this case is unusual documenting LHON in association with PRES.

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L eber hereditary optic neuropathy (LHON) is a maternally inherited mitochondrial disorder, characterized by sequential occurrence of acute or subacute bilateral visual loss and centrocecal scotomas. In most patients, there are no other neurologic manifestations, and neuroimaging of the brain is normal. However, additional neurologic features rarely have been described including the occurrence of LHON and multiple sclerosis (MS) (1–3). We describe a patient with symptoms compatible with LHON, confirmed by genetic testing, who also had reversible bilateral occipital lesions associated with headache and epileptic seizures.

CASE REPORT

A 13-year-old boy developed blurred vision in his both eyes. He was the firstborn child of a healthy nonconsanguineous Chinese couple, and the family history was unremarkable. The patient initially was diagnosed with bilateral optic neuritis and underwent intravenous pulse methylprednisolone therapy without improvement in vision.

Forty-seven days after the onset of symptoms, the patient complained of headache followed by 4 generalized tonic-clonic seizures. His blood pressure was normal, and there was no history of a seizure disorder. He was diagnosed with viral encephalitis and treated with acyclovir (50 mg every 8 hours for 2 weeks) and phenytoin (200 mg 3 times a day). Subsequently, he had no further seizures.

On day 75 after the onset of symptoms, he was referred to our Neurology Department for further evaluation. Visual acuity was 20/400 bilaterally, visual fields showed central scotomas in each eye, and both optic discs were pale. Neurologic examination was otherwise normal.

No evidence of abnormality was not found in complete blood count, urinalysis, biochemistries, including erythrocyte sedimentation rate and C reaction protein. Markers of autoimmune diseases were negative and included antinuclear antibody, antineutrophil cytoplasmic antibody, anticardiolipin antibodies and rheumatoid factor. Examination of the cerebrospinal fluid (CSF) on 2 occasions was unremarkable. Serum and CSF viral antibody tests were negative for herpes simplex virus (HSV-1 and HSV-2), varicella zoster virus, Epstein-Barr virus, and measles virus. Viral polymerase chain reaction was not done on the CSF. Electroencephalography was normal.

Magnetic resonance imaging (MRI) of the brain performed 42 days after the symptom onset, and prior to seizures, was normal. Five days following the onset of seizures, MRI revealed high signal intensity lesions
involving the occipital lobes on both T2 and fluid-attenuated invasion recovery (FLAIR) images (Fig. 1A). Diffusion-weighted imaging showed no evidence of restricted diffusion. Sixteen days after the onset of seizures, there was partial resolution of the signal change in both occipital lobes (Fig. 1B), and by 34 days, MRI was normal in appearance (Fig. 1C).

In evaluating our patient, we were suspicious of a mitochondrial disorder including LHON and mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS). Muscle biopsy (left brachial biceps) was performed, and no ragged red fibers were found. Screening mitochondrial DNA (mtDNA) for 3 primary LHON point mutations revealed a homoplasmic mtDNA G11778A mutation in lymphocytes. MELAS mtDNA point mutations (A3243G and A3271T) were absent. Large-scale rearrangements of mtDNA extracted from muscle were screened for Southern blotting of DNA and were not found. Sequencing the entire mtDNA coding region excluded rare mutations associated with MELAS, myoclonic epilepsy with ragged red fibers, or LHON/MELAS syndrome. No other pathogenic mutations were found in all mtDNA transfer RNA, complex I, complex III, complex IV, and complex V genes except for G11778A mutation. The diagnosis of LHON was established, and the patient was treated with coenzyme Q10.

The presence of the G11778A mutation was confirmed in our patient’s younger brother, who is clinically unaffected. The mother of the proband is asymptomatic and refused evaluation.

DISCUSSION

While the clinical presentation and results of genetic testing secured the diagnosis of LHON in our patient, the occurrence of seizures with LHON is rare (1,4). Serial brain MRI in our case revealed complete resolution of abnormal T2 and FLAIR signal changes in the occipital lobes, consistent with posterior reversible encephalopathy syndrome (PRES).

PRES is characterized by seizures, altered mental state, headache, focal neurologic deficits, and visual disturbances (5–7). Cerebral edema most often is detected in the parieto-occipital region but may occur in the temporal lobe, temporal-occipital junction, cerebellum, and, rarely, in the basal ganglia and brainstem. It commonly occurs at the border zones of cerebral arterial territories. Hypertension is the most frequent predisposing cause of PRES, but the syndrome has been reported in a wide variety of settings, including solid organ transplantation and medications used to prevent rejection, renal disease, autoimmune disorders, severe infection, and mitochondrial disorders (8,9). The etiology of PRES in our patient is unclear.

Headache and seizures also may occur in stroke-like episodes of MELAS. In addition, LHON/MELAS overlap phenotype associated with a complex I or complex V subunit gene mutation had been reported (10,11). However, our patient did not have ragged red fibers on muscle biopsy, and the sequence analysis of entire mtDNA coding region revealed no other pathogenic mutations in all mtDNA transfer RNA, complex I, complex III, complex IV, and complex V genes.

The most common mutations of LHON are missense mutation in mitochondrial encoded complex I subunits, which are 11778 G>A, 3460 G>A, and 14484 T>C. All of these mtDNA mutations have been reported to be associated with white matter disorders typically in a periventricular distribution resembling MS (4,12–15). Several pathogenic mechanisms have been proposed: 1) impairment of cellular energy generation with ATP depletion; 2) this energy crisis causes lipid peroxidation and oxidative damage of protein, causing damage to the mitochondrial membrane; 3) altered mitochondrial permeability leads to initiation of apoptotic cell death; and 4) vascular changes with the accumulation of abnormal mitochondria in both endothelial and smooth muscle cells of the blood vessel walls (15,16). Magnetic resonance spectroscopy studies of LHON with the G11778A mutation have demonstrated abnormal mitochondrial energy metabolism in the occipital lobe (17). Grazina et al (12)
reported that in individuals harboring the 11778G>A mutation, possible association with other neurologic disturbances may be explained by heteroplasmy, different tissue distribution of mutant mtDNA, and other genomic and environmental modifiers. It may be that a variety of these factors contributed to the unusual clinical course of our patient.

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Perineural Optic Nerve Enhancement on Magnetic Resonance Imaging in Giant Cell Arteritis

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Abstract: Giant cell arteritis (GCA) may cause visually devastating optic neuropathy. In atypical cases, diagnosis of optic neuropathy can be delayed. We present 2 such atypical cases and demonstrate that contrast-enhanced orbital magnetic resonance imaging may be a valuable tool in patient evaluation and aid in the diagnosis of GCA.

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At times, patients with giant cell arteritis (GCA) may present without classic signs and symptoms. For example, in arteritic posterior ischemic optic neuropathy (PION), the fundus, including the optic disc, appears normal (1). This may lead to delay in diagnosis and treatment, often with devastating consequences. We evaluated 2 patients who illustrate this clinical conundrum and demonstrate the utility of dedicated fat-suppressed contrast-enhanced orbital magnetic resonance imaging (MRI) in the workup of unexplained vision loss in GCA.

CASE REPORTS

Case 1
An 83-year-old woman presented to her primary care physician with headache and blurred vision in her right eye. Visual acuity was hand motions, right eye, and 20/30, left eye. Funduscopy was normal bilaterally. Erythrocyte sedimentation rate (ESR) was 36 mm/hour with a platelet count of 494,000/mm³ (normal range: 150,000–400,000/mm³). C-reactive protein (CRP) was not obtained. Because GCA was suspected, the patient was given 250 mg of methylprednisolone intravenously every 6 hours beginning 90 minutes after ophthalmic examination. She was examined 14 hours later and found to have vision of hand motion, right eye, and light perception, left eye. The fundus examination remained unremarkable in both eyes. The patient received intravenous steroids for 3 days and then was switched to 60 mg of prednisone daily.

The normal fundus appearance, with rapid progression of bilateral vision loss despite aggressive steroid treatment and normal ESR, prompted consideration of causes other than GCA. While brain MRI was normal, a dedicated orbital study demonstrated bilateral perineural optic nerve enhancement (Fig. 1). Additional workup for autoimmune, inflammatory, and neoplastic etiologies including cerebrospinal fluid analysis was nondiagnostic. Temporal artery biopsy showed focal infiltration of the media with lymphocytes and multinucleated giant cells, consistent with GCA. Four days later, visual acuity was no light perception in the right eye and light perception in the left eye. Over the following 2 weeks, visual acuity deteriorated to no light perception in both eyes, and remained unchanged over several months as her prednisone was gradually tapered.

Case 2
A 68-year-old woman was evaluated by her local eye care provider with a 1-day history of blurred vision in her left eye. Visual acuity was 20/20, right eye, and 20/25, left eye. There was a left relative afferent pupillary defect and automated perimetry was normal in the right eye and showed superior and inferior arcuate defects in the left eye. The right fundus was normal, whereas the left fundus reportedly showed pallid optic disc swelling with disc elevation with peripapillary hemorrhages.

Laboratory testing included ESR of 10 mm/hour, CRP of 1.1 ng/dL (normal range: 0.0–4.9 mg/dL) and platelet count of 202,000/mm³ (normal range: 150,000–400,000/mm³).
Acuity in the left eye declined to hand motions. Believed to have nonarteritic anterior ischemic optic neuropathy, the patient was referred nonurgently for neuro-ophthalmic evaluation.

When seen in consultation 2 weeks later, visual acuity was 20/20, right eye, and no light perception, left eye. The right fundus was unremarkable, whereas the left disc was pale. The patient was treated with 60 mg of prednisone daily, and temporal artery biopsy was scheduled. Brain MRI with contrast was normal, but an orbital study revealed perineural enhancement of the left optic nerve (Fig. 2). Based on imaging studies, the patient was admitted to the hospital for further workup and given 1 g of methylprednisolone intravenously daily for 5 days and then placed on 60 mg of prednisone per day. Temporal artery biopsy showed lymphohistiocytic infiltrate and disruption of the internal elastica consistent with GCA. During 1 year of follow-up, the patient’s vision has remained stable and her prednisone dosage has been gradually reduced.

**DISCUSSION**

Enhancement of the optic nerve on MRI may involve the nerve itself or the surrounding meninges. Optic nerve enhancement has been reported in a variety of disorders including optic neuritis (2,3), carcinomatous meningitis (3,4), idiopathic orbital inflammation (5), sarcoidosis (6), Wegener granulomatosis (7), and radiation-induced optic neuropathy (2).

In contrast, perineural optic nerve enhancement is detected much less frequently. It has been described in optic perineuritis (nonspecific inflammation) (8), sarcoidosis (6), Wegener granulomatosis (7), syphilis (9), herpes zoster, and tuberculosis (10). In addition, there are 2 published reports of perineural enhancement in patients with GCA. Lee et al (11) described an 82-year-old woman with classic symptoms of GCA who had no light perception, left eye, with pallid optic disc edema. MRI revealed perineural enhancement of the left optic nerve, and temporal artery biopsy was consistent with GCA. Morgenstern et al (12) reported an 83-year-old man who presented with visual acuity of no light perception, left eye, with pallid optic disc edema. MRI revealed perineural enhancement of the left optic nerve, and temporal artery biopsy was consistent with GCA. Morgenstern et al (12) reported an 83-year-old man who presented with visual acuity of no light perception, right eye, and 20/50, left eye. He had bilateral pallid optic disc swelling, and MRI showed enhancement of both optic nerve sheaths and adjacent orbital fat. Positive temporal artery biopsies were obtained during his evaluation. In addition, biopsy of the right optic nerve sheath showed inflammation of the perineural vasculature with multinucleated giant cells and disruption of the internal elastic lamina.

**FIG. 1.** Case 1. Postcontrast axial (A) and coronal (B) T1 magnetic resonance imaging with fat suppression shows perineural enhancement of both optic nerves (arrows).

**FIG. 2.** Case 2. Contrast-enhanced axial (A) and coronal (B) T1 magnetic resonance imaging with fat suppression demonstrate perineural enhancement of the left optic nerve (arrows).
It seems likely that arteritic PION played a role in the visual loss experienced by our patients. We propose that retrobulbar perineurial enhancement signifying disruption of the blood–optic nerve barrier results from primary inflammation, secondary ischemia, or both. In our cases, the perineural pattern of the enhancement suggests that the more highly vascularized meningeal components of the nerve were preferentially affected. Inflammation in GCA injures endothelial cells that can increase vascular permeability of the paracellular and transcellular transport pathways regulated, in part, by endothelial tight junctions (13). Morgenstern et al (12) have demonstrated active inflammation in the meshwork of pial vessels surrounding the optic nerve. The blood–optic nerve barrier can become highly permeable (14,15) and the optic nerve sheath expresses major histocompatibility complex class II cells that participate in antigen presentation in the inflammatory cascade (16). Retinal vessels preferentially seem to be spared in patients with GCA. It has been proposed that the retina is an “immune-privileged” organ, with retinal pigmented epithelial cells having several means of suppressing host immune responses (17–19). Thus, the breach of the blood–optic nerve barrier, but not the blood–retinal barrier, might explain why enhancement is restricted to the perineural space of the optic nerve.

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Background: A number of cerebrovascular disorders produce manifestations of neuro-ophthalmologic significance. In many cases, these disorders can be treated using endovascular techniques.

Methods: The material in this article was obtained from a combination of personal experience and review of the literature using PubMed.

Results: A variety of new equipment, materials, and techniques are available to the interventional neuro-radiologist dealing with intracranial vascular lesions such as aneurysms, arteriovenous fistulas, and arteriovenous malformations.

Conclusion: Physicians whose patients have intracranial vascular lesions should be aware of the endovascular options available for their patients.

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A wide variety of orbital and intracranial disorders of neuro-ophthalmologic significance have the potential to be or are currently being treated by new and emerging interventional neuroradiologic techniques. In this review, some of the most important of these are discussed.

PSEUDOTUMOR CEREBRI ASSOCIATED WITH VENOUS SINUS STENOSIS

Pseudotumor cerebri (PTC) refers to a condition in which there is increased intracranial pressure (ICP) in the absence of primary cerebral disease on conventional imaging associated with cerebrospinal fluid (CSF) that contains no evidence of an infectious, inflammatory, or malignant process. Although the cause of PTC in some patients is medication, such as lithium, or an underlying systemic condition, such as systemic lupus erythematosus, most patients have no apparent underlying disease. These patients are said to have a form of PTC called “idiopathic intracranial hypertension” (IIH). Patients with PTC (including those with IIH) usually become symptomatic with severe headache and papilledema, with some patients progressing to permanent vision loss. Patients who present with evidence of an optic neuropathy or who experience progressive visual loss despite maximum medical therapy can be extremely difficult to manage and often require surgery (optic nerve sheath fenestration, shunting procedures) and prolonged courses of narcotics or other analgesic medications.

Venous sinus stenosis may play a role in the pathogenesis of so-called IIH, but the exact mechanism remains a topic of widespread debate. Nevertheless, up to 90% of patients with otherwise typical IIH demonstrate either unilateral or bilateral transverse–sigmoid sinus stenosis, suggesting that stenosis is a potential etiology (1).

Venous sinus stenting is possible with the advent of stents that are sufficiently flexible to permit navigation of the intracranial venous sinuses. Multiple publications have documented the efficacy of venous sinus stenting for the treatment of IIH, although there are no clinical trials that have compared this treatment with weight loss alone, medical therapy (e.g., acetazolamide), with or without weight loss, or other types of surgery (e.g., optic nerve sheath fenestration; ventriculopertoneal, ventriculoatrial, or lumboventricular shunts) (2–13). In any event, these reports, including our own (13), have documented a reduction of ICP with resolution of headache, tinnitus, and papilledema in at least 80% of treated individuals. However, some patients develop re-stenosis just proximal to the stent and others have persistent headaches that are not related to persistently elevated ICP but rather to a form of migraine as they resolve with anti-migraine medication (11,13).

At our institution, we perform computed tomographic venography (CTV) before and after lumbar puncture with removal of sufficient CSF to normalize ICP in patients with...
presumed IIH. If there is venous sinus stenosis and the stenosis disappears after normalization of ICP, we conclude that the increased ICP caused the stenosis, and we treat the patient with standard medical therapy or surgery. However, if, upon normalization of ICP, the stenosis remains, then we consider whether to stent the patient. In some cases, we will use medical therapy (i.e., acetazolamide) first and stent only if there is no clinical improvement; in other cases, particularly those in which an optic neuropathy is already present, we will perform stenting.

Our procedure for venous sinus stenting is as follows. At this time, only patients with progressive optic neuropathy under maximal medical therapy are considered as potential candidates for endovascular therapy. If bilateral stenosis is confirmed by CTV after lumbar puncture (Fig. 1A), the patient is scheduled for endovenous manometry under general anesthesia. A diagnostic cerebral angiogram is performed first to rule out the presence of other vascular anomalies, in particular a dural vascular fistula that could mimic the presentation of IIH. This arterial access will also provide the “roadmap” images necessary for navigation of endovascular devices within the cranial venous system. Venous access is obtained by percutaneous femoral puncture. A long sheath (90 cm long; 6-French Shuttle sheath, Cook, IN) is inserted, and its distal tip brought into the left internal jugular vein, immediately below the skull base. A 3-French microcatheter (Renegade hi-flo; Boston Scientific, Natick, MA) is carefully advanced through the sheath into the cranial venous system. Endovascular navigation is performed using the roadmap technique. The microcatheter is advanced across the torcular and the left transverse sinus into the right internal jugular vein. An exchange-length microwire (300 cm, 0.014 in Luge wire; Boston Scientific), advanced into the left internal jugular vein though the microcatheter, is kept across both transverse sinus stenoses to offer a platform for subsequent stent placement. The microcatheter is connected to a pressure line, and measurements are obtained in each segment of dural sinus as it is progressively pulled back into the right internal jugular vein. If a pressure gradient higher than 4 mm Hg is recorded, stenting is performed (Fig. 1B). To date, the right transverse sinus has been targeted in all our patients (15 cases). Our group uses a self-expandable nitinol stent (Precise, Cordis). Our institutional review board has approved the off-label application of this carotid stent, and the off-label nature of the treatment is fully disclosed to the patient and recorded on the consent form. Bilateral pressure measurements are repeated after stent deployment. The patient is admitted to our neuroscience critical care unit for overnight observation. Antiplatelet therapy using a combination of aspirin and abciximab, started 5 days before the procedure, is maintained for 6 months, after which abciximab is discontinued.

CENTRAL RETINAL ARTERY OCCLUSION

Central retinal artery occlusion (CRAO) occurs in 1 per 10,000 ophthalmology out-patient visits (14). The visual prognosis of CRAO is poor with 61% of patients having a final visual acuity (VA) of 20/400 or worse (15). This degree of severe unilateral visual impairment is associated with limitations in social functioning, poor mental health (16), and is a risk factor for becoming dependent (17). Most CRAOs are thought to be thrombotic or embolic (18). Standard therapies for CRAO include ocular massage, paracentesis, and other methods of reducing intraocular pressure as well as inhalation of a mixture of 95% oxygen and 5% carbon dioxide (carbogen). These treatments have not been shown conclusively to improve VA beyond the natural history of disease (19,20).

Systemic and intra-arterial thrombolysis have been successful in restoring perfusion to ischemic tissue by fibrin–platelet clot lysis in ischemic stroke and myocardial infarction (21–23). Several small series have reported long-term significant improvement in VA with local intra-arterial or intravenous fibrinolysis, particularly when therapy was begun within 12 hours after the onset of visual loss (24–28). However, to date, there is only one randomized, prospective clinical trial comparing intra-arterial fibrinolysis (IAF) with “conventional” therapy.

FIG. 1. Bilateral transverse sinus stenosis. A 37-year-old woman with idiopathic intracranial hypertension had worsening papilledema despite maximum medical therapy. A. Computed tomographic venography (CTV) obtained after normalization of the cerebrospinal fluid pressure by lumbar puncture confirms bilateral transverse sinus stenosis (arrows). B. CTV obtained 6 months after stenting the right transverse sinus shows that the treated segment is patent. The patient’s papilledema resolved within 4 weeks.
The European Assessment Group for Lysis in the Eye (EAGLE) trial found no difference in visual outcome in patients treated with “conservative” techniques plus IAF compared with patients who received only “conservative” therapy (29). In addition, there were more complications in the IAF-treated group than in the conservatively treated group, and this is one of the reasons that the trial was halted prematurely. It must be noted, however, that in this trial, “conservative” therapy consisted of a 5-day course of anticoagulation using heparin (this therapy did not include paracentesis). This is not the standard therapy in the United States, and the acute anticoagulation received by both groups of patients may have been an equalizing factor. Although IAF is NOT the standard of care for patients with a CRAO, we have treated a number of patients with IAF with reasonable results and do not believe that the EAGLE trial should necessarily preclude such treatment. We believe that a trial of “conservative” therapy without heparinization may be appropriate in some patients, whereas in others, particularly those who are seen within 6 hours after visual loss, intra-arterial fibrinolysis should be considered.

Our procedure for intraarterial fibrinolysis is as follows. The patient is brought to the neuroangiography suite as soon as the diagnosis of CRAO has been confirmed. Although most procedures are performed under conscious sedation, elderly patients or patients unable to lie flat may need general anesthesia. Femoral arterial access is obtained and a guiding catheter (usually a 5-French system) is brought to the common carotid artery ipsilateral to the affected eye. Biplane angiography is performed to document the appearance of the cerebral circulation; this baseline angiogram will serve as a reference for comparison with the final angiogram obtained at the end of the procedure. This initial angiogram also provides important information about the cranio-cervical arterial anatomy, documenting in particular the presence of atheromatous lesions along the endovascular access route (carotid bifurcation, distal internal carotid artery [ICA]), the degree of patency of the ophthalmic artery, and the existence of potential anatomic variants influencing the treatment strategy (e.g., an ophthalmic artery originating from the middle meningeal artery). The guiding catheter is then advanced into the ICA (providing there is no significant atheromatous disease at the bifurcation, in which case the guide would be kept in the common carotid artery), and a microcatheter (usually a 1.7-French system) is advanced to the clinoid segment of the ICA. Several techniques can then be adopted to access the ophthalmic artery, depending on its size and anatomy, the presence of ostial atheromatous disease, and the operator’s preference. In our practice, superselective catheterization is performed using an over-the-wire technique, in which the microwire (usually 0.010 inches in diameter) is advanced into the ophthalmic artery and the microcatheter threaded over the wire until it sits in a stable position within the artery, just past its proximal bend. This preferred location is not always attainable, and the microcatheter tip must at times be left at the ostium of the artery. In such cases, the tip of the microcatheter is left abutting the dorsal wall of the ICA just proximal to the ophthalmic artery origin, with the hope that flow preferentially will direct the lytic agent into the targeted artery. The lytic agent (recombinant tissue plasminogen activator [r-tPA], 1 mg/mL) is administered slowly though the microcatheter using hand injections with 3-mL syringes, with a maximum dose of 20 mg of r-tPA (Fig. 2). At the end of the procedure, a common carotid angiogram is obtained and compared with the baseline angiogram to detect potential intracranial complications. Patients typically are kept in our neuroscience critical care unit for overnight observation.

**DIRECT CAROTID-CAVERNOUS SINUS FISTULAS**

A direct carotid-cavernous sinus fistula (CCF) results from a single tear in the wall of the cavernous segment of the ICA. This produces a direct connection between the artery and one or more of the venous channels within the cavernous sinus. The arteriovenous connection usually is short, tangential, and endothelialized (30–32). It is identical in anatomy and

FIG. 2. Endovascular treatment 8 hours after a central retinal artery occlusion. A. Lateral view of a digital subtraction angiography shows selective injection of the right ophthalmic artery. Arrow indicates the site of origin of the right ophthalmic artery. This injection was performed through a 1.9F microcatheter (outside diameter of 0.63 mm). Note stagnation of contrast and lack of filling of intraorbital arteries. B. After administration of 10 mg of tissue plasminogen activator, the ophthalmic artery and its branches appear normal. The patient experienced visual recovery within minutes of the thrombolysis.
hemodynamics, with traumatic arteriovenous fistulas elsewhere in the body.

The direction of blood flow through a direct CCF may be posterior, into the superior and inferior petrosal sinuses, or anterior, into the orbital veins. Although posteriorly draining fistulas occasionally cause isolated oculomotor cranial nerve pareses, the most severe oculomotor manifestations occur in patients with anterior redirection of arterial blood through normal orbital venous channels. These manifestations are caused by a combination of diminished arterial flow to the cranial nerves within the cavernous sinus, stasis of both venous and arterial circulation within the eye and orbit, and an increase in episcleral and orbital venous pressure. Typical signs of a direct CCF include an objective and/or subjective bruit, proptosis, chemosis, “arterialization” of conjunctival and episcleral vessels, ophthalmoplegia from neural and/or mechanical mechanisms, increased intraocular pressure, and ischemic retinopathy. Patients in whom the fistula causes arterial drainage into the cerebral veins and sinuses are at risk for intracranial hemorrhage. Accordingly, most direct CCFs require treatment.

Endovascular closure is the most common method used to close a direct CCF and most often is accomplished by embolization using a variety of agents, primarily platinum coils and detachable balloons (33–37). These materials usually are introduced into the cavernous sinus through the ICA, but in selected cases, they may be introduced either transvenously through the inferior petrosal sinus, pterygoid plexus, or the superior ophthalmic vein, or directly into the cavernous sinus via a craniotomy, transethmoidal transsphenoidal approach, or even a direct puncture through the superior orbital fissure (38–43).

At our institution, we use a variety of techniques for endovascular closure of a direct CCF. Most commonly, the cavernous sinus will be closed with detachable microcoils. The access route can be either transvenous, for example, via the superior ophthalmic vein, the pterygoid plexus, or one of the petrosal sinuses, or transarterial with the microcatheter reaching the cavernous sinus through the carotid wall injury (Fig. 3).

When successful, patients experience dramatic improvement in symptoms and signs almost immediately, although it may take months for their complete resolution. In all cases, standard femoral access followed by diagnostic cerebral angiography is obtained to document the anatomy of the lesion and the presence of potential sources of collateral supply if carotid sacrifice has to be contemplated. In addition, a transvenous approach requires venous access, most commonly obtained by puncture of a femoral vein. These procedures are performed at our institution under general anesthesia. Alternate techniques have been used, in which the cavernous sinus is filled with a liquid embolic agent, or in the past, with detachable balloons. In some instances of direct CCF secondary to a ruptured aneurysm, selective coiling of the aneurysm alone is sufficient to close the fistula, whereas in cases where the ICA is extensively damaged, occlusion of the cavernous sinus with sacrifice of the carotid artery may have to be performed. In some of these instances, flow-diverting stents provide another endovascular option.

**DURAL CAROTID-CAVERNOUS SINUS (ARTERIOVENOUS) FISTULAS**

These lesions are actually congenital arteriovenous fistulas that develop spontaneously, often in the setting of atherosclerosis, systemic hypertension, connective tissue disease, and during or after childbirth. Dural CCFs consist of a communication between the cavernous sinus and one or more meningeal branches of the ICA, the external carotid artery, or both (44). Fistulas involving branches from both the internal and the external carotid arteries are the most common.

Dural CCFs usually have low rates of arterial blood flow. Nevertheless, they can produce significant visual and neurologic deficits similar to those caused by direct CCFs. Although many dural CCFs close spontaneously and others produce only minor visual symptoms and signs and thus do not require treatment, those that produce significant ocular or neurologic manifestations require closure (Fig. 4).

Endovascular procedures, including transarterial embolization, transvenous embolization, or a combination of these procedures, can be used with variable success, but they are an option only when the fistula is accessible through the ICA.

**FIG. 3.** Endovascular treatment of a direct carotid-cavernous sinus fistula. **A.** Lateral view of digital subtraction angiogram following left common carotid injection reveals carotid-cavernous sinus fistula. An irregularity of the dorsal wall of the left internal carotid artery (ICA) suggests the possibility of an aneurysm (arrow) that has ruptured into the cavernous sinus. **B.** After coiling, there is complete eradication of the fistula with preservation of normal flow in the left ICA and its branches.
techniques, usually are the optimum treatment for dural CCFs that produce progressive or significant symptoms and signs, including visual loss, diplopia, an intolerable bruit, severe proptosis, and, most importantly, cortical venous drainage (45). A number of synthetic and natural materials can be used for embolization. Platinum coils are most often used, but other materials include absorbable gelatin (Gelfoam); Silastic; low-viscosity silicone rubber; autogenous clot, muscle or dura; tetradecyl sulfate (a sclerosing agent); polyvinyl alcohol particles (Ivalon); ethanol; ethylene vinyl alcohol copolymer (Onyx), oxidized cellulose (Oxycel); various preparations of cyanoacrylate glue; or a combination of these (46).

In patients with a fistula fed only by meningeal branches of the external carotid artery, the embolization material is introduced via a microcatheter placed in the external carotid artery and passed into the specific branch or branches that feed the fistula. In this setting, successful closure of the fistula is almost always possible, resulting in rapid resolution of all symptoms and signs. When the fistula is fed by meningeal branches from both the external carotid artery and the ICA, only the branches from the external carotid artery usually are embolized in the hopes that the flow to the fistula will be sufficiently decreased to result in its subsequent closure. The ICA usually is not embolized unless the interventionalist can successfully catheterize the meningohypophysial trunk or other meningeal feeders from the artery. If the fistula does not close with this technique, it often can be treated subsequently via a transvenous route. In this setting, and in patients whose fistulae are fed only by meningeal branches from the ICA, the favored transvenous approach usually is via the femoral or internal jugular vein into the ipsilateral or rarely the contralateral inferior or superior petrosal sinus and from there into the cavernous sinus (46–52). If this approach fails, a variety of other approaches may be used, most of which involve cannulation of the superior or inferior ophthalmic veins (53–55).

The superior ophthalmic vein approach is performed in most cases by surgical exposure of the vessel. All procedures are performed in a neurosurgical operating room under fluoroscopic guidance. With the patient under general anesthesia, a sheath is placed in a common femoral artery to permit intraoperative angiography. Following prepping and draping of the affected eye and orbital regions, the superior ophthalmic vein is accessed via a transcutaneous incision. A segment of it is isolated between 2 sutures, and a microcatheter, the size of which is determined by the diameter of the vein, is placed into an opening in the vein and threaded into the cavernous sinus under fluoroscopic guidance; platinum coils are detached in the cavernous sinus until the fistula is closed as determined by intraoperative angiography. The catheter is withdrawn, the superior ophthalmic vein is permanently occluded using bipolar cautery and ligatures, and the skin incision is closed (48,49,51,56–60). In some cases, more than one session and more than one approach is needed, and in rare cases, the cavernous sinus can be cannulated directly via an orbital approach (57,61). Using currently available techniques, successful closure of dural CCFs can be achieved in 80%–100% of patients (52,53,62–65).

Complications of endovascular treatment of dural CCFs are uncommon except in patients with connective tissue disorders such as Ehlers-Danlos syndrome (66,67). Nevertheless, significant complications have been reported, including hemorrhage at the catheter site, in the orbit from perforation of the superior or inferior ophthalmic vein, or even intracranially; damage to orbital structures such as the trochlea when the superior ophthalmic vein is used for access to the cavernous sinus; local infection; sepsis; ophthalmic artery occlusion; and both transient and permanent neurologic deficits, particularly facial pain and ocular motor cranial nerve pareses, and brainstem infarction.

FIG. 4. Endovascular treatment of a dural carotid-cavernous (arteriovenous) fistula in an 84-year-old woman with spontaneous occurrence of right periorbital swelling, redness, and proptosis and recent or old history of trauma. A. Lateral view of digital subtraction angiogram, right common carotid injection, shows a right-sided dural arteriovenous fistula of the cavernous sinus that drains into the orbital venous system and inferior petrosal sinus. The lesion is fed by multiple extradural branches of the right internal carotid and external carotid arteries. B. After treatment using a transcutaneous, transvenous approach through the superior ophthalmic vein, there is obliteration of the fistula.
FIG. 5. Treatment of a paraophthalmic aneurysm with stent-assisted coiling. A. Digital subtraction angiogram, left common carotid injection, shows a 5-mm right ophthalmic segment saccular aneurysm (arrow). B. Three-dimensional digital subtraction angiogram shows that the neck of the aneurysm is quite broad and the origin of the ophthalmic artery (arrow) is separate from the aneurysmal sac (arrowhead). C. Unsubtracted lateral view of the region of the aneurysm as the self-expanding stent (4.5 mm by 22 mm) is being deployed. The distal stent markers (arrow) are visible, indicating that this portion of the stent is now applied to the wall of the right internal carotid artery (ICA). The stent extends both proximally and distally well beyond the neck of the aneurysm. A second microcatheter that will be used subsequently to deliver the coils has been placed within the aneurysm (tip indicated by arrowhead). D. Subtracted, right anterior oblique projection shows partial obliteration of the aneurysm after placement of 3 microcoils (arrow). A final control angiogram after 6 microcoils documented total obliteration of the lesion. E. Subtracted right anterior oblique projection, obtained during a 1-year follow-up study, confirms eradication of the aneurysm with preservation of flow in the right ICA.
An analysis of 4 large series of patients with dural CCFs treated endovascularly revealed that of a total of 339 patients, there were complications in 35 (10.3%) (46,52,53,62). Because the embolization techniques used to close dural CCFs can be associated with vision-threatening and even life-threatening complications, physicians performing such procedures should explain to the patient not only the benefits but also the risks of these procedures and must be prepared to deal with them should they occur (70,72).

**OPHTHALMIC ARTERY SEGMENT ANEURYSMS**

Aneurysms arising from the ICA at the origin of or just distal to the ophthalmic artery are termed ophthalmic artery segment aneurysms (73). These aneurysms project dorsally or dorsomedially from the surface of the ICA toward the temporal aspect of the ipsilateral optic nerve (73,74).

The surgical treatment of ophthalmic artery segment aneurysms is both challenging and complex because of their close proximity to the anterior clinoid process and the optic nerves as well as the need to exclude the lesion from the intracranial circulation while maintaining patency of the parent vessel (73–78). Fortunately, refinements in microsurgical techniques and greater understanding of regional anatomy have made surgery of these aneurysms less formidable (79–81). In addition, endovascular therapy has evolved in the last decade to become an effective alternative to microsurgical clipping of these lesions (82–85). In particular, flow-diverter devices consisting of porous tubular tight mesh have been used with good success (86), as well as with aneurysms in other locations (87). Even when ophthalmic segment artery (OSA) aneurysms are treated successfully, procedure-related vision loss remains a significant risk regardless of the modality of treatment, including stents and flow diverters (88–91).

At the Johns Hopkins Hospital, we use a consensus-based approach to determine the treatment of patients with OSA aneurysms. All patients with unruptured OSA aneurysms are discussed at a weekly conference attended by vascular neurosurgeons, neurologists, neuro-ophthalmologists, and neurointerventionalists. For patients for whom endovascular intervention is recommended, the technique is as follows. All interventional procedures are performed under general anesthesia. Following femoral arterial access, a 6-French guide catheter is advanced over a 0.035 guidewire into a stable position in the ICA. Pre-embolization digital subtraction angiography (DSA), including 3-dimensional...
imaging, is then performed (Fig. 5A, B). Under roadmap guidance, a microcatheter is placed within the aneurysmal sac. Patients with an unfavorable sac–neck ratio in whom placement of a stent (e.g., Enterprise, Cordis Neurovascular; Neuroform, Boston Scientific; Pipeline, Covidien) (Fig. 5C) is anticipated are placed on a regimen of aspirin and clopidogrel at least 3 days before the procedure. Aneurysm coiling is performed using various brands of detachable microcoils. All patients are heparinized during treatment using activated clotting time monitoring. Control angiography is performed to monitor progress (Fig. 5D) and at the end of the procedure to ensure obliteration of the aneurysm and patency of the parent vessel and the rest of the intracranial circulation (Fig. 5E). Patients are admitted to the Intensive Care Unit for overnight observation; heparinization is continued for 24 hours.

The balloon remodeling technique can be used as an alternative to stent placement in wide-necked ophthalmic segment and other aneurysms. In this technique, the balloon is positioned across the aneurysm neck and transiently inflated during each microcoil placement (Fig. 6). This is particularly useful in patients with ruptured aneurysms, in whom preparation with antiplatelet therapy is not advisable (a loading dose of aspirin and clopidogrel can be given at the time of a stent procedure but in our practice, it is only given after the stent has been deployed). The aneurysm cavity is filled with microcoils of various sizes and configurations until a satisfactory result has been achieved. Patients typically are observed overnight in the neuroscience critical care unit and a second night in a regular floor bed. Aspirin usually is continued indefinitely in all patients, regardless of the technique used to treat the aneurysm, and, in patients in whom a stent has been placed, are treated with clopidogrel for 6 months, at which time a follow-up angiogram usually is obtained.

A recent review of 101 ophthalmic artery segment aneurysms treated at our institution, using a consensus-based approach, demonstrated that regardless of the treatment modality, there is a significant risk of vision loss (91). Twenty-nine patients (33%) had what appeared to be either a new visual deficit or a worse visual deficit after treatment, and no patient with pre-existing visual loss experienced vision improvement postoperatively. Factors associated with postoperative vision loss were greater aneurysm size, pretreatment aneurysm rupture, pre-existing visual loss, and aneurysm re-treatment. Specifically, giant aneurysms, 7 (32%) of 22 large aneurysms, and 15 (19.5%) of 77 small aneurysms occurred in the group of patients that experienced visual deficits. Nineteen (21%) of 92 unruptured aneurysms were in this group. Five (83%) of 6 patients with pre-existing visual symptoms experienced worsening of their vision posttreatment. Vision loss postcoiling may result from emboli to the optic nerve or retina, an increase in mass effect from excessive coil packing, a water-hammer effect from inadequate coil packing, or coil-related peri-aneurysmal inflammation that may or may not respond to systemic corticosteroids (83,91–93).

CAVERNOUS SINUS ANEURYSMS (UNRUPTURED)

Aneurysms arising from the cavernous portion of the ICA may produce a variety of neurological deficits, primarily those related to vision, including diplopia from single or multiple ocular motor nerve pareses, decreased VA from compressive or ischemic optic neuropathy, corneal and facial anesthesia or hypesthesia from involvement of the trigeminal nerve, and facial pain (94). Like other intracranial aneurysms, these

**FIG. 7.** Treatment of a cavernous aneurysm with a flow diverter. **A.** Digital subtraction angiogram, lateral view, shows a large saccular aneurysm of the cavernous segment of the left internal carotid artery (ICA). **B.** The aneurysm was treated by placing 3 overlapping flow-diverting stents (Pipeline, eV3) in the artery as shown on a DynaCT scan (lateral view). **C.** Digital subtraction angiogram, lateral view, left common carotid injection 6 months after treatment indicates obliteration of the aneurysm with preservation of the left ICA and its branches (Courtesy of Dr. Mohammad Ali Aziz-Sultan, University of Miami, Florida).
Aneurysms can rupture, but this is a rare event and when it occurs, usually does not produce a subarachnoid or intracerebral hemorrhage because of the cavernous location of the aneurysm (95,96). Rupture of a cavernous sinus aneurysm (CCA) usually causes a CCF or, rarely, epistaxis (96,97).

Although most intracranial (intradural) aneurysms can be treated surgically or with endovascular techniques that isolate them from the parent vessel without occluding that vessel, this is more difficult with CCAs (97). In the past, the treatment of CCAs required occlusion of the ipsilateral ICA with its attendant risks of stroke, blindness, or both (98,99). Endovascular techniques such as stenting alone using a pipeline or similar device (Fig. 7), stenting and coiling (Fig. 8), and balloon remodeling can be used successfully to occlude the aneurysm, with the precise technique used depending on the anatomy of the lesion, including its shape, size, and the manifestations it is producing.

At our institution, the protocol for endovascular treatment of CCAs is as follows. Procedures are performed under general anesthesia. Patients are placed on antiplatelet therapy (aspirin and clopidogrel) at least 5 days before the procedure, as a preparation for possible stent placement and/or balloon remodeling. Femoral arterial access is obtained (6-French system) and intravenous heparin administered (aiming for ACT value between 250 and 300 sec). A baseline cerebral angiogram is performed. In addition, three-dimensional DSA images are used to measure the size of both the aneurysm and its parent artery, to choose appropriately size microcoils and/or stent, and also to determine the best angiographic projections for the procedure. A 6-French guiding catheter is advanced into the ICA under roadmap guidance, and a microcatheter placed into the aneurysmal cavity. Various types of microcatheters are available; the most commonly used ones vary in size between 1.9 and 2.3 French. If the use of a stent followed by coiling is contemplated (wide-necked aneurysms), the stent can be deployed while the microcatheter is already in place within the aneurysmal cavity (“jailing technique” most commonly used at our institution) or, alternatively, the microcatheter can be advanced into the aneurysm with the stent already deployed (the latter technique having the potential disadvantage, in our opinion, of moving the stent if accessing the aneurysm is not straightforward). The balloon remodeling technique can be used as an alternative to stent placement in wide-necked cavernous aneurysms in the same way as for intradural aneurysms (see above). In our practice and regardless of the technique used to occlude the aneurysm, patients are observed overnight in the neuroscience critical care unit, and a second night in a regular floor bed. Aspirin is usually continued indefinitely in all patients who undergo embolization of an aneurysm, and, in addition, patients in whom a stent...
is placed are treated with clopidogrel for 6 months. A follow-up angiogram usually is obtained 6 months after treatment.

**OCCIPITAL LOBE ARTERIOVENOUS MALFORMATION**

Arteriovenous malformations (AVMs) are the most common form of intracranial vascular hamartoma. The incidence in unselected populations is about 1 in 100,000 per year (100). AVMs occur slightly more often in men than in women, with a ratio of about 1.4:1. The majority of intracranial AVMs occur as an isolated sporadic phenomenon; however, familial cases have been described. As AVMs are congenital, they can become symptomatic at any age (101). In the majority of patients (70%), they do not produce symptoms until the second or third decade of life and frequently present during puberty. The data on arteriovenous malformation (AVM) hemorrhage during pregnancy are controversial and inconclusive, and there is no evidence that cesarean section is better than vaginal delivery (102).

There is no consistent correlation between the location, size, and structural peculiarities of intracranial AVMs and their clinical manifestations (103); however, most occipital AVMs produce signs of intracerebral or subarachnoid hemorrhage, seizures, or visual manifestations, all of which may be associated with headaches that often are similar to or identical with migraine with or without visual aura (104,105). In most large series, hemorrhage is a more common presenting manifestation than seizures or isolated neurologic symptoms and signs, regardless of the age of the patient, but the actual percentages vary considerably. AVMs account for 1%–2% of strokes, 9% of subarachnoid hemorrhages, 4% of primary intracerebral hemorrhages, 1% of unprovoked seizures, and 0.3% of isolated headaches. The long-term annual fatality rate is probably 1%–1.5%, with an annual rate of initial bleed of about 2% (100).

*FIG. 9.* Endovascular treatment of an occipital arteriovenous malformation (AVM) in a 48-year-old woman with severe headaches and a left superior homonymous quadrantanopia. Axial (A) and coronal (B) T1 magnetic resonance imaging shows changes consistent with a right occipitotemporal AVM. C. Lateral view of digital subtraction angiogram, right vertebral artery injection, shows a large AVM fed by multiple branches from the right posterior cerebral artery and principally draining into the right transverse sinus via the right vein of Labbé. D. Subtracted angiogram, right external carotid artery injection, reveals a smaller posterior nidal compartment with separate venous drainage toward the superior sagittal sinus. The decision was made to treat the anterior compartment with endovascular techniques and the posterior one with radiosurgery. E. Lateral subtracted view after 3 endovascular sessions shows that the right posterior cerebral branches have been embolized using a liquid embolic agent (NBCA glue). There is no residual opacification of the nidus from this vessel. Neuro-ophthalmological evaluation postembolization showed the visual field defect to be stable. F. Axial computed tomographic image, obtained after embolization, shows the distribution of the radio-opaque NBCA glue within the AVM nidus.
As noted above, most AVMs in the occipital region present with visual symptoms; however, the precise location of most AVMs, unlike tumors, has no close correspondence with the resulting neurologic symptoms and signs. This may be the result of circulatory disturbances in neighboring areas of the brain due to steal by the AVM from normal vascular channels. In addition, the manifestations of occult AVMs may result from spread of seizure discharge or from the destructive effects of intracranial hemorrhage or increased ICP. Transient attacks of unformed photopsias in the right or left homonymous field of vision may occur by themselves or as an aura of a seizure. Transient homonymous hemianopia is a related phenomenon (98,100).

Occipital lobe AVMs may be discovered in 1 of 4 settings: 1) after an intracranial hemorrhage, 2) after a seizure, 3) in the course of an investigation of progressive or acute focal or generalized neurologic dysfunction, including an isolated homonymous field defect, and 4) fortuitously during an evaluation for an unrelated abnormality. Risk factors for bleeding identified in various retrospective series include patient-related factors (e.g., hypertension, previous hemorrhage), and angioarchitectural features (e.g., intranidal aneurysm, deep venous drainage, high feeding artery pressure, deep/periventricular location, flow-related aneurysm, venous stenosis, slow filling of feeding arteries, and nidus size) (100,103).

Depending on their manifestations, size, feeding vessels, and drainage, occipital lobe AVMs may be observed without intervention, resected, embolized, treated with stereotactic radiosurgery, embolized and then resected, or embolized and then treated with radiosurgery (Fig. 9) (106,107). A number of synthetic and natural agents are available for embolization, including Gelfoam (absorbable gelatin) powder and sponge, collagen (Avitene), Silastic, steel or fiber platinum coil, electrolytically detachable coils (Gugliemi detachable coils), low-viscosity silicone rubber, autogenous clot, muscle or dura, tetracycl sulfates (a sclerosing agent), polyene threads, polyvinyl alcohol (Ivalon), absolute ethanol, oxidized cellulose (Oxycel), isobutyl-2-cyanoacrylate (bucrylate), and n-butylcyanoacrylate. These latter 2 agents are liquid adhesive materials of low viscosity that polymerize rapidly upon contact with blood. In addition, embolization using latex or silicone detachable and calibrated-leak balloons also may be used in appropriate cases.

At our institution, all patients with occipital lobe AVMs undergo a neuro-ophthalmologic assessment before treatment, and all are advised of the potential for development of a new homonymous field defect or worsening of a previous incomplete defect. They are also advised as to the visual implications of such a defect, particularly if it is complete (e.g., inability to drive). Embolization of an occipital lobe AVM is performed as follows. Depending on the patient’s age and size, 4-, 5-, or 6-French systems are used. The posterior cerebral artery (PCA) is generally accessed via one of the vertebral arteries, except when it originates predominantly from the ICA (fetal origin of the PCA). Additional supply from the middle cerebral artery must be considered in larger lesions. Embolization of cerebral AVMs with liquid embolic agents in a multimodality context is our preferred approach. This means that embolization is usually not performed with a curative goal in mind but as a preparation to either surgery or radiosurgery. We believe that this multimodality approach offers the best chances of successful therapy with the lowest possible complication rate. However, in favorable instances, cure can be achieved by endovascular means alone. Various interventional techniques can be applied to the embolization of cerebral AVMs. Procedures are performed under general anesthesia, and our patients are heparinized (ACT 250–300 sec), with the exception of ruptured AVMs treated acutely. Thanks to the recent improvements in catheter and wire technology, we believe that flow-guided and over-the-wire systems are equally safe in most situations, and the latter option generally is used in our practice. A liquid embolic agent, in our practice NBCA glue, is injected within the AVM nidus or, if this optimal position cannot be achieved, as close as possible to the nidus, after detailed angiographic analysis of the feeding artery anatomy to exclude the presence of normal arterial branches (Fig. 9). Procedures are staged to prevent posttreatment cerebral edema and hemorrhages secondary to the normal perfusion breakthrough phenomenon (108).

We use a maximum embolization goal of 30%–50% of the nidus per session. Intranidal high-flow arteriovenous shunts and/or intra/juxtanidal aneurysms are generally targeted during the initial sessions. The microcatheter and the guiding catheter are withdrawn simultaneously after each glue injection, and new systems are used for each superselective embolization. New formulation of the NBCA glue and improvement in devices (e.g., hydrophilic coating) have tremendously decreased the risk of glueing the tip of the microcatheter in place, a complication always feared but never observed in our practice. Patients are extubated at the end of the procedure and observed overnight in the intensive care unit. Staged treatments are usually performed at 6- to 8-week intervals.

It should be clear from this review that the field of interventional neuroradiology is changing rapidly with new techniques, refinements of old techniques, new instruments, and new materials. All physicians who manage patients with vascular lesions, such as those described, must have a close working relationship with a neurointerventionalist so that such patients can receive optimum care.

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An Elderly Woman With Difficulty Reading and Abnormal Eye Movements

Virginie Desestret, MD, PhD, Nathalie Streichenberger, MD, PhD, Muriel Panouillères, Denis Pélisson, PhD, B. Plus, MD, Charles Duycikaerts, MD, PhD, Dennis K. Burns, MD, Christian Scheiber, MD, PhD, Alain Vighetto, MD, Caroline Tilikete, MD, PhD

Dr Tilikete

A 73-year-old woman was evaluated in our neuro-ophthalmology clinic with a 1-year history of progressive difficulty reading. The patient’s visual acuity, pupillary reactions to light and near stimulation, visual fields, and fundus were normal. Examination of her eye movements revealed a supranuclear vertical gaze abnormality, characterized by lack of upward saccades but intact downward saccades. The patient also had had difficulty initiating voluntary, especially leftward horizontal saccades on command, but reactive horizontal saccades were relatively well preserved. She was able to follow a pencil light moved by the examiner using small saccades (saccadic smooth pursuit) and her vestibulo-ocular reflex (VOR) was intact. She had apraxia of lid closure. The patient had no cognitive deficit, behavioral or social disturbance, aphasia, alexia, limb apraxia, postural ataxia, pyramidal signs or parkinsonism.

Neuropsychological testing was hindered by reading difficulties but disclosed mild attentional and executive deficits, with verbal memory and language conserved (Table 1). Saccades were recorded (500 Hz; EyeLink II eye-tracker; SR Research, Mississauga, Canada) during a paradigm of reactive saccades toward 8 degrees right or left and a paradigm of voluntary scanning saccades during simultaneous presentation of three targets (−8, 0, and +8 degrees). VOR during pendular chair stimulation (maximum velocity: 40 degrees per second, frequency: 0.25 Hz) and smooth pursuit (target amplitude: 30 degrees, frequency: 0.15 Hz) were recorded using 25-Hz infrared video-oculography (VNG Ulmer; Synapsys, Marseille, France).

The VOR was normal with preservation of the rightward and leftward quick phases (reflexive saccades) (Fig. 1A). Smooth pursuit showed saccadic following of the target (Fig. 1B). Reactive saccades to the right (Fig. 1C; Table 2) and left (Fig. 1D; Table 2) had normal latency and amplitude. Voluntary scanning saccades presented abnormal latency, specifically to the left (Fig. 1E, F; Table 2). Neuro-imaging included magnetic resonance imaging (MRI) of the brain, a SPECT scan, and a DaTscan. This last study is a SPECT scan for striatal dopamine transporter visualization.

Dr Scheiber

The brain MRI shows only frontal cortical atrophy without brainstem atrophy (Fig. 2A, B), and the standard SPECT study demonstrates bilateral frontal and left parietal hypoperfusion (Fig. 2C, D). The DaTscan shows bilateral nigrostriatal dopamine transporter loss (Fig. 2E).

Dr Tilikete

The patient was diagnosed with an acquired ocular motor apraxia and supranuclear vertical ophthalmoplegia, presumably from some type of degenerative process. There were no other signs of Parkinson disease or progressive supranuclear palsy (PSP). The differential diagnosis included fronto-temporal lobar degeneration (FTLD) and cortico-basal degeneration.
TABLE 1. Neuropsychological evaluation

<table>
<thead>
<tr>
<th>Cognitive Function</th>
<th>Testing Technique</th>
<th>Testing Results</th>
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<tbody>
<tr>
<td>Verbal memory</td>
<td>Californian Verbal Learning Test (1)</td>
<td>Delayed recall: 11/16, Total recall: 48/80, Recognition performance: 15/16</td>
</tr>
<tr>
<td>Language</td>
<td>Protocol of Bachy-Langedock (2)</td>
<td>34/36</td>
</tr>
<tr>
<td>Visuospatial function, visual–motor integration</td>
<td>Figures copies/praxia</td>
<td>Score: 3/3</td>
</tr>
<tr>
<td>Attentional functions, executive functions</td>
<td>Digits span (3)</td>
<td>Digits backward: 3</td>
</tr>
<tr>
<td></td>
<td>Trail making test (4) A trial: 148 sec, &lt;10th percentile; B trial: not evaluable Coloras 47; 10’ recall: 45</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stroop interference task (5)</td>
<td>Animals per minute: 17, P-words per minute: 6</td>
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<tr>
<td>Verbal fluency</td>
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A vascular process was considered unlikely in view of the MRI findings.

Subsequently, the patient developed bucco-facial apraxia, severe dysarthria, swallowing apraxia, and total vertical ophthalmoaplegia, retaining dissociation between reactive and voluntary horizontal saccades. There was no postural imbalance, dementia, or signs of lower motor neuron disease (MND). Following her death 3 years after the initial presentation, a postmortem examination was performed according to the BrainNet Europe Consortium protocol (6). Autopsy consent was obtained in accordance with French and European regulations.

**Dr Burns**

The unfixed brain weighed 1,035 g and showed severe cortical atrophy affecting the fronto-temporal and parietal lobes. The basal nuclei and hippocampus showed less severe reduction in bulk. Pigmentation of the substantia nigra was normal. The cerebellum, cerebral peduncles, pontine base, medullary pyramids, and cervical spinal cord were unremarkable.

An impressive histological feature visible in the sections of the cortex stained with hematoxylin and eosin is the presence of spongiform change, most conspicuous in the superficial cortical regions. Spongiform change is a feature of a number of different diseases, including neurodegenerative disorders, ischemia, and prion disease. Involvement of superficial cortical layers is characteristic of several neurodegenerative disorders, including Alzheimer disease and FTLD. Immunohistochemical staining for various abnormal protein aggregates has become an essential part of the evaluation of FTLD and other neurodegenerative disorders. In the present case (Fig. 3), immunohistochemical evaluation demonstrates ubiquitin, TDP43, and the ubiquitin-binding protein p62 in the cytoplasm of both neurons and glial cells and within neuropil threads in the posterior frontal cortex, motor neurons in the brainstem (hypoglossal nucleus), and spinal cord, and in brainstem nuclei, including the rostral mesencephalic premotor oculomotor region. Ubiquitin reactivity is also present in neurons and neuropil threads in the pars compacta of the substantia nigra and in striatal fibers. No convincing TDP43 or ubiquitin reactivity is identified within the dentate gyrus of the hippocampus. The distribution of abnormal TDP43 and ubiquitin reactivity places this case in the category of TDP43/ubiquitin-related FTLD with MND, a variant of FTLD that is often, but not invariably, associated with signs and symptoms of MND.

**Final Diagnosis**

FTLD of FTLD-TDP subtype 2, according to Sampathu FTLD classification (7).

**Dr Tilikete**

Our patient presented with a reading disorder that was related to a rare form of acquired, progressive oculomotor apraxia suggestive of frontal lobe dysfunction. Acquired oculomotor apraxia is clinically defined by loss of voluntary control of saccades and pursuit, with preservation of reflexive eye movements, including slow and quick phases (reflexive saccades) of vestibular nystagmus (i.e., VOR) (8). Conservation of VOR slow phases and preservation of quick phases pointed to impaired cortical control of eye movements. The loss of initiation of saccades in this case was thought to reflect bilateral disruption of the descending neuronal oculomotor pathways from the frontal (FEF) and parietal (PEF) eye fields (9). The prominent alteration of leftward saccades suggested predominant right hemisphere involvement, and the dissociated preservation of reactive saccades supported a prominent involvement of the (right) FEF pathway (10).

This oculomotor disturbance corresponds to the mirror-model of the psychic paralysis of gaze or gaze apraxia observed in Balint syndrome, secondary to bilateral posterior parietal lobe lesions, in which voluntary saccades may be more easily initiated than reactive saccades (11). Clinical examination also revealed an upward vertical saccadic palsy, with preservation of downward saccades, vertical smooth pursuit, and VOR, consistent with a supranuclear vertical ophthalmoaplegia. The absence of upward quick phases suggested tegmental brainstem involvement of premotor oculor...
motor neurons (8). This progressive upward vertical ophthalmoplegia associated with apraxia of lid closure met the criteria for possible PSP (12); however, the prominent ocular motor apraxia in our patient differed from the more subtle impaired control of voluntary saccades (antisaccade errors) usually seen in patients with PSP (13).

The clinical discrepancies between our patient’s signs of FTLD and those of PSP were consistent with the lack of

**TABLE 2.** Gain and latency measurements (±SD) for rightward and leftward reactive and voluntary saccades

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rightward</th>
<th>Leftward</th>
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<tbody>
<tr>
<td>Gain</td>
<td>0.81 ± 0.05 (n = 21)</td>
<td>0.84 ± 0.05 (n = 20)</td>
</tr>
<tr>
<td>Latency (ms)</td>
<td>205 ± 19 (n = 21)</td>
<td>254 ± 27 (n = 20)</td>
</tr>
<tr>
<td>Gain</td>
<td>0.82 ± 0.32 (n = 26)</td>
<td>0.52 ± 0.26 (n = 15)</td>
</tr>
<tr>
<td>Latency (ms)</td>
<td>564 ± 332 (n = 26)</td>
<td>1060 ± 521 (n = 15)</td>
</tr>
</tbody>
</table>
FIG. 2. Neuroimaging. Axial fluid-attenuated inversion recovery (A) and contrast-enhanced T1 sagittal (B) magnetic resonance imagings show frontal cortical atrophy without brainstem atrophy. No vascular or mass lesions are present. Sagittal (C) and coronal (D) brain SPECT scans reveal evidence of posterior frontal and left parietal hypoperfusion (arrows). Dat-SPECT imaging (E) discloses bilateral nigrostriatal dopamine transporter loss (arrows).

FIG. 3. Neuropathological findings. A. The neocortices show gliosis and a variable degree of microvacuolation (hematoxylin and eosin). Immunohistochemical staining for ubiquitin, p62, and TDP-43 reveals numerous round glial (GCIs) and neuronal (NCIs) intracytoplasmic inclusions in the upper laminae of the frontal, temporal, and parietal cortices and in the striatum. B. TDP-43–positive NCIs. C. GCIs in striatal fiber fascicles which, on high magnification, contain coiled body–like TDP-43–positive oligodendroglial inclusions. TDP-43–positive NCIs and threads are present in brainstem nuclei, including the rostral mesencephalic premotor oculomotor region containing the interstitial nucleus of the medial longitudinal fascicle (D) and in anterior horn motor neurons (E). Skein-like and round NCIs are present in large neurons in the hypoglossal nucleus (F, G). Comma-shaped TDP-43–positive neurites were observed in the substantia nigra (H). Scale bars: 20 μm.
neuropathologic features of PSP. FTLD includes various neurodegenerative diseases characterized by selective degeneration of the frontal and temporal lobes. Neuropathologically, FTLD is associated with distinct pathological patterns, mainly abnormal accumulation of tau protein (FTLD-tau) or ubiquitin inclusions (FTLD-U subtype) (14). In FTLD-U, the majority of cases, as in our patient, show TDP-43 (TAR DNA-binding protein-43)–positive inclusions (FTLD-TDP) (15). Subtle and asymptomatic frontal ocular motor impairment (decreased horizontal saccade gain and increased antisaccade errors) and PSP-like eye movement abnormalities have been demonstrated in FTLD, usually later in the clinical course (13,16,17). Primary symptomatic ocular motor impairment in FTLD is unusual.

We found abnormal inclusions in the rostral portions of the medial longitudinal fasciculus, the premotor ocular motor relay for vertical saccades (18). These findings could explain the PSP-like supranuclear ophthalmoplegia. FTLD-TDP lesions were present in the FEs as well as in modulators of the descending supranuclear pathways (striatum and substantia nigra). These findings would explain the patient’s ocular motor apraxia.

Pathological analysis confirmed FTLD-MND, characterized by FTLD with TDP-43 inclusions, in a patient who did not develop signs of lower MND nor fronto-temporal dementia. According to Sampathu FTLD classification (7), this case was subtype 2, which often also exhibits TDP-43–positive inclusions in both upper and lower motor neurons (19). Motor neuron involvement is consistent with the high incidence of MND in these patients (20); however, clinical features of MND or dementia may be lacking in patients belonging to the neuropathological spectrum of FTLD-MND (21,22). The presence of specific inclusions in the hypoglossal nuclei but not in the ocular motor nuclei is also classically described in FTLD-MND patients (23). This pathological selectivity is partially explained by the fact that the TDP-43 proteinopathy may only affect nuclei that receive direct projections from cortical areas (24). The pathophysiological vulnerability of some neuronal populations may determine the clinical phenotype.

In conclusion, ocular motor apraxia previously has not been described as a predominant clinical syndrome associated with FTLD. The findings in our patient broaden the clinical picture of FTLD with TDP-43 immunoreactive inclusions to include primary progressive ocular motor apraxia.

ACKNOWLEDGEMENT

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REFERENCES


Erratum


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REFERENCE
Literature Commentary


Objectives: Magnetic resonance imaging (MRI)–based measurements used to diagnose progressive supranuclear palsy (PSP) typically lack pathologic verification and are not easy to use routinely. We aimed to develop in histologically proven disease a simple measure of the midbrain and pons on sagittal MRI to identify PSP.

Methods: Measurements of the midbrain and pontine base on T1 midsagittal MRI were performed in confirmed PSP (n = 12), Parkinson disease (n = 2), and multiple system atrophy (MSA) (n = 7), and in controls (n = 8). Using receiver operating characteristic curve analysis, cutoff values were applied to a clinically diagnosed cohort of 62 subjects that included PSP (n = 21), Parkinson disease (n = 10), MSA (n = 10), and controls (n = 21).

Results: The mean midbrain measurement of 8.1 mm was reduced in PSP (P < 0.001) with reduction in the midbrain to pons ratio (PSP smaller than MSA; P < 0.001).

In controls, the mean midbrain ratio was approximately two-thirds of the pontine base, in PSP it was <52%, and in MSA the ratio was greater than two-thirds. A midbrain measurement of <9.35 mm and ratio of 0.52 had 100% specificity for PSP. In the clinically defined group, 19 of 21 PSP cases (90.5%) had a midbrain measurement of <9.35 mm.

Conclusions: We have developed a simple and reliable measurement in pathologically confirmed disease based on the topography of atrophy in PSP with high sensitivity and specificity that may be a useful tool in the clinic.

Neurodegenerative diseases with Parkinsonism have overlapping features and are sometimes difficult to diagnose with clinical certainty. Previous studies distinguishing progressive supranuclear palsy (PSP) from multiple system atrophy (MSA) have provided useful magnetic resonance imaging (MRI) guidance, such as the “hummingbird” sign in PSP, not seen in MSA. However, there is little pathologic verification of the diagnoses in previous studies. The current study looked at the anterior-posterior diameter of the midbrain and pons and a ratio of the 2 brainstem regions and correlated these findings to histopathology. The measures were highly reliable at distinguishing PSP from MSA and are more reassuring because of the pathologic confirmation.

—Mark L. Moster, MD

I recently saw a 56-year-old woman who was diagnosed with a cerebellar ataxia by the referring neurologist, but he noted that her smooth pursuit was not normal. She had been falling for a few years and her speech was mildly slurred. Her saccades were slowed, especially in the vertical plane, and she failed the 3-clap test. My impression was that she likely had very early PSP, but the neurologist was not too excited about that diagnosis. Since PSP is a clinical diagnosis, it can be challenging to convince both patients and providers of it in the early stages.

After reading this article, I went back and measured her midsagittal brain MRI. Her midbrain was 8.8 mm, and her midbrain to pons ratio was 47%, further supporting my initial impression. The methodology is straightforward, and it took me less than 5 minutes to measure. This could represent a high-yield finding.

—Michael S. Lee, MD


Objective: To assess the value of enhanced depth imaging optical coherence tomography (EDI OCT) in diagnosing and evaluating optic nerve head drusen (ONHD) compared with conventional diagnostic methods.

Design: Prospective, comparative, cross-sectional study.

Participants: Thirty-four patients with clinically visible or suspected ONHD in either eye based on dilated optic disc examination or optic disc stereophotography and without ocular comorbidity.

Methods: Spectral-domain OCT of the optic nerve head in both conventional (non-EDI) and EDI modes, ultrasound B-scan, and standard automated perimetry were performed on both eyes of all participants.

Main Outcome Measures: Detection and findings of ONHD between EDI OCT and conventional diagnostic methods.
Results: Sixty-eight eyes were clinically classified into 3 groups: 32 eyes with definite ONHD, 25 eyes with suspected ONHD, and 11 normal-appearing fellow eyes. In the definite ONHD group, EDI OCT, non-EDI OCT, and ultrasound B-scan were positive for ONHD in all eyes, and visual field (VF) was abnormal in 24 eyes. In the suspected ONHD group, EDI OCT, non-EDI OCT, ultrasound B-scan, and VF were positive in 17, 14, 7, and 3 eyes, respectively; 8 eyes had no evidence of ONHD in any of the tests. In normal-appearing fellow eyes, EDI OCT, non-EDI OCT, ultrasound B-scan, and VF were positive in 3, 1, 1, and 0 eyes, respectively; 4 eyes had no evidence of ONHD in any of the tests. Enhanced depth imaging OCT had a significantly higher ONHD detection rate than ultrasound B-scan in all eyes (52/68 eyes vs 40/68 eyes; $P < 0.001$), in eyes with clinically suspected ONHD or normal-appearing fellow eyes (20/36 eyes vs 8/36 eyes; $P < 0.001$), and in eyes with clinically suspected ONHD (17/25 eyes vs 7/25 eyes; $P = 0.002$). Enhanced depth imaging OCT-detected ONHD appeared as signal-poor regions surrounded by short, hyper-reflective bands or isolated/clustered hyporeflective bands without a signal-poor core. In non-EDI OCT, posterior surfaces of the ONHD and deep-seated hyper-reflective bands were invisible or less clear than in EDI OCT.

Conclusions: Enhanced depth imaging OCT detects lesions likely representing ONHD more often and better assesses their shape and structure than conventional tests.

At a recent neuro-ophthalmologist meeting, I heard a speaker say that one should obtain a B-scan ultrasound for children suspected of papilledema. She stated that if it were normal, then the child should undergo neuroimaging and a lumbar puncture, suggesting that B-scan should easily identify optic nerve head drusen (ONHD).

Enhanced depth imaging optical coherence tomography is a specialized algorithm on the Spectralis OCT (Heidelberg Engineering, Germany), which improves imaging of deeper structures in the posterior segment. The authors compared the ability of non-EDI OCT, EDI-OCT, and B-scan ultrasound to identify ONHD among patients with definite ONHD, clinically suspicious ONHD, and normal appearing optic discs. Among the clinically suspicious and normal appearing optic discs with ONHD, EDI-OCT identified ONHD significantly better (20/20) than the non-EDI OCT (15/20) and B-scan ultrasound (8/20) among the groups with clinically suspicious and normal-appearing optic discs. None of the ONHD detected by ultrasound or non-EDI OCT were missed by the EDI-OCT.

The authors describe the EDI-OCT findings of subtle ONHD as clusters of hyper-reflective bands posterior to Bruch membrane. Generally speaking, these subtle ONHD did not appear on ultrasonography. I would highly recommend taking a look at the figures to see exactly what they mean and how the ONHD appear using EDI-OCT. They are well worth studying, and I could envision future speakers stating that a child with suspected papilledema should undergo EDI-OCT (rather than B-scan) to evaluate for ONHD.

—Michael S. Lee, MD

Advances in OCT technology continue to enhance the expertise of the clinician. The images in this article convincingly show ONHD and are reassuring that the patient does not have papilledema. The ability to demonstrate ONHD definitively at the time of clinical examination relieves the stress and cost of a workup for papilledema. EDI-OCT in this preliminary study was better than our previous “gold standard” of ultrasonography for demonstrating ONHD.

—Mark L. Moster, MD


Among 249 patients with teratoma-associated encephalitis, 211 had N-methyl-D-aspartate receptor antibodies and 38 were negative for these antibodies. While antibody-positive patients rarely developed prominent brainstem-cerebellar symptoms, 22 (58%) antibody-negative patients developed a brainstem-cerebellar syndrome, which in 45% occurred with opsoclonus. The median age of these patients was 28.5 years (12–41), 91% were women, and 74% had full recovery after immunotherapy and tumor resection. These findings uncover a novel phenotype of paraneoplastic opsoclonus, which until recently was likely considered “idiopathic” or “postinfectious”. The triad, young age—teenager—young adult), systemicteratoma, and high response to treatment characterize this novel brainstem-cerebellar syndrome.

The differential diagnosis of patients with opsoclonus most often includes parainfectious, paraneoplastic or idiopathic. This article moves some patients from the idiopathic category to the paraneoplastic group. The syndrome of brainstem-cerebellar dysfunction, often with opsoclonus, was seen in 38 patients with teratoma (mostly benign). This contrasts with the group of 211 with teratoma who had antibodies to the NMDA receptor and presented with psychosis or other behavioral abnormalities and dyskinesias. The brainstem-cerebellar
presentation preceded the diagnosis of teratoma in 82%. Treatments included tumor resection, immunotherapy (pulsed IV methylprednisolone, IVIg). A teenager or young adult with a brainstem cerebellar syndrome, including opsoclonus, should now be evaluated for teratoma. These patients are older than most with neuroblastoma and younger than those with lung cancer.

—Mark L. Moster, MD

Let us also not forget that brainstem encephalitis with oposconus-myoclonus can also result from anti-Ri, Ma2, Hu, and amphiphysin associated with breast and ovarian cancer, small-cell lung cancer, and pediatric neuroblastoma. There is a nice review on evaluation of paraneoplastic disorders including teratomas from a European Federation of Neurological Societies task force (1). The article recommends transvaginal ultrasound as the first-line investigation for teratoma followed by computed tomography of the pelvis.

—Michael S. Lee, MD


In myasthenia gravis (MG), the neuromuscular junction is impaired by the antibody-mediated loss of postsynaptic acetylcholine receptors (AChRs). Muscle weakness can be improved on treatment with pyridostigmine, a cholinesterase inhibitor, or with 3,4-diaminopyridine, which increases the release of ACh quanta. The clinical efficacy of pyridostigmine is in doubt for certain forms of myasthenia. Here we formally examined the effects of these compounds in the antibody-induced mouse model of anti–muscle-specific kinase (MuSK) MG. Mice received 14 daily injections of IgG from patients with anti-MuSK MG. This caused reductions in postsynaptic AChR densities and in endplate potential amplitudes. Systemic delivery of pyridostigmine at therapeutically relevant levels from days 7–14 exacerbated the anti-MuSK-induced structural alterations and functional impairment at motor endplates in the diaphragm muscle. No such effect of pyridostigmine was found in mice receiving control human IgG. Mice receiving smaller amounts of MuSK autoantibodies did not display overt weakness, but 9 days of pyridostigmine treatment precipitated generalized muscle weakness. In contrast, 1 week of treatment with 3,4-diaminopyridine enhanced neuromuscular transmission in the diaphragm muscle. Both pyridostigmine and 3,4-diaminopyridine increase ACh in the synaptic cleft, yet only pyridostigmine potentiated the anti–MuSK-induced decline in endplate ACh receptor density. These results thus suggest that ongoing pyridostigmine treatment potentiates anti–MuSK-induced AChR loss by prolonging the activity of ACh in the synaptic cleft.

In the healthy neuromuscular junction, MuSK may help promote growth of postsynaptic AchR, while acetylcholine may contribute to AchR pruning. Studies have suggested that patients with anti-MuSK MG may experience worsening with pyridostigmine use. In a series of elegant experiments, the authors showed that treatment with pyridostigmine worsened the findings in mice receiving anti-MuSK IgG injections: (1) mice became weaker clinically, (2) the endplate potential (EPP) amplitude of the diaphragm declined, and (3) AChR density declined compared to untreated mice receiving injections of anti-MuSK IgG.

Normally, 3,4-DAP acts by increasing the number of Ach quanta released from the presynaptic terminal compared to pyridostigmine, which increases the duration of Ach within the cleft. Treatment with 3,4-DAP had no effect on clinical weakness or AchR density, but did improve EPP amplitude. This suggests that the synergistic effect of anti-MuSK IgG and pyridostigmine on AchR loss occurs from prolonged exposure of Ach rather than quantity of Ach.

Clinically, sometimes I treat patients suspicious for MG with pyridostigmine before the laboratory testing results come back. This article will make me consider avoiding pyridostigmine among patients with bulbar symptoms who may be suspicious for anti-MuSK MG. I can understand that pyridostigmine can be ineffective in MuSK-positive patients, but who would have thought it could be detrimental?

—Michael S. Lee, MD

Michael, I would be very hesitant to make any clinical practice changes based on this article. First, the authors did not study mice treated with acetylcholine receptor antibodies (AchRAb), so one may not conclude that there are different effects of pyridostigmine in MuskAb MG patients than in AchRAb MG patients. Second, the dosages used in this study are well more than commonly used therapeutic doses in humans or in animal studies. Most of my patients are on 180–360 mg/d of pyridostigmine, up to approximately 5 mg/kg/d, well below the 16 mg/kg/d in this study. It is well known that even in AchRab MG, clinical AchRAb patients, worsening occurs with...

Importance: Recognition of sagging eye syndrome (SES) as the cause of chronic or acute acquired diplopia may avert neurologic evaluation and imaging in most cases.

Objectives: To determine whether SES results from inferior shift of lateral rectus (LR) extraocular muscle (EOM) pulleys and to investigate anatomic correlates of strabismus in SES.

Design and Setting: We used magnetic resonance imaging to evaluate rectus EOMs, pulleys, and the LR-superior rectus (SR) band ligament at an eye institute.

Participants: Patients with acquired diplopia suspected of having SES. We studied 56 orbits of 11 men and 17 women (mean [standard deviation] age, 69.4 [11.9] years) clinically diagnosed with SES. Data were obtained from 25 orbits of 14 control participants age-matched to SES and from 52 orbits of 28 younger controls (23 [4.6] years).

Main Outcome Measures: Rectus pulley locations compared with age-matched norms and lengths of the LR-SR band ligament and rectus EOMs. Data were correlated with facial features, binocular alignment, and fundus torsion.

Results: Patients with SES commonly exhibited blepharoptosis and superior sulcus defect. Significant inferolateral LR pulley displacement was confirmed in SES, but the spectrum of abnormalities was extended to peripheral displacement of all other rectus pulleys and lateral displacement of the inferior rectus pulley, with elongation of rectus EOMs (P < 0.001). Symmetrical LR sag was associated with divergence paralysis esotropia and asymmetrical LR sag greater than 1 mm with cyclovertical strabismus. The LR-SR band was ruptured in 91% of patients with SES.

Conclusions and Relevance: Widespread rectus pulley displacement and EOM elongation, associated with LR-SR band rupture, causes acquired vertical and horizontal strabismus. Small-angle esotropia or hypertropia may result from common involutional changes in EOMs and orbital connective tissues that may be suspected from features evident on external examination.

This is an important article. It further expands the narrative that Joseph Demer, MD, has been developing regarding orbital causes of diplopia not because of neurologic illness and that occur with increasing frequency with aging. Currently many neuro-ophthalmologists perform MRIs on patients presenting with divergence insufficiency and most often do not find abnormalities that alter the treatment. If additional studies support the concept that benign structural changes in the orbit may cause diplopia, we may reach the point where, in many instances, imaging of the brain is no longer necessary.

—Mark L. Moster, MD

Interestingly, the authors did not actually define what constituted a diagnosis of SES. In the introduction and the discussion, I get the impression that it is defined by a “sag” or inferior displacement of the lateral rectus pulley, which leads to the clinical findings and also requires MRI to define. Clinically, these patients may have ptosis, deep superior sulcus, or high eyelid creases. The horizontal ductions and saccadic speeds should be normal, but there may be a divergence insufficiency pattern. Others may exhibit vertical strabismus with significant unilateral or bilateral elevator palsy.

To me, I would not feel comfortable diagnosing SES and avoiding neuroimaging especially in a patient who has ptosis and an elevator palsy on the same side as shown in one of their figures. Instead, I see the greatest value in their MRI findings. If I order neuroimaging in such a patient, I would look for the elongation of the EOM and centrifugal displacement of the rectus pulleys. I do not know if the MRI would be good enough to see rupture of the LR-SR band, but I would look for it. The MRI findings could help confirm the diagnosis of SES as the probable causes of diplopia.

—Michael S. Lee, MD


Purpose: To evaluate the role of oral corticosteroids as an anti-inflammatory adjunct in the treatment of orbital cellulitis.

Design: Prospective, comparative, single-masked, interventional clinical study.

Methods: Setting: tertiary eye care center (All India Institute of Medical Sciences). Study population: patients with acute pyridostigmine overdosage, so we must use caution with this medication.

—Mark L. Moster, MD

I would agree with you, however it does give one pause that the clinical worsening could result from AchR loss caused by the pyridostigmine use. I think further study is necessary, but to me, it is an unexpected finding.

—Michael S. Lee, MD
onset (within 14 days) of orbital cellulitis with or without abscess. **Intervention:** patients were randomized into 2 groups in the ratio of 1:2. Both groups received initial intravenous antibiotics. In Group 2, oral steroids were added after an initial response to intravenous antibiotics. **Main outcome measures:** resolution of signs and symptoms, duration of intravenous antibiotics, length of hospital stay, and sequelae of disease (ptosis, proptosis, and movement restriction) were evaluated and compared between the 2 groups.

**Results:** A total of 21 patients (age range, 11–59 years) with orbital cellulitis were studied. There were 7 patients in Group 1, who received standard intravenous antibiotics, and 14 in Group 2, who received adjuvant steroids. Patients in Group 2 showed an earlier resolution of inflammation in terms of periorbital edema ($P = 0.002$ at day 7), conjunctival chemosis ($P < 0.001$ at day 10), and pain ($P = 0.012$ at day 7). They also attained vision of 0.02 on logarithm of the minimum angle of resolution earlier than Group 1 patients. Decrease in proptosis and improvement in extraocular movements were also significantly better with the use of steroids ($P = 0.027$ at day 10, $P = 0.003$ at day 14, respectively). While a significant number of patients in Group 1 had mild residual ptosis, proptosis, and movement restriction at 12 weeks, none of the patients treated with steroids had any residual changes ($P = 0.023$, $P = 0.001$, and $P = 0.001$, respectively). The durations of intravenous antibiotics and hospital stay were significantly less in Group 2.

**Conclusions:** Use of oral steroids as an adjunct to intravenous antibiotic therapy for orbital cellulitis may hasten resolution of inflammation with a low risk of exacerbating infection.

In this study, if patients responded to intravenous antibiotics within the first 3 days, oral prednisone was begun at 1.5 mg/kg/d for 3 days, followed by 1 mg/kg/d for 3 days, then tapered over 1–2 weeks. I was a bit surprised to hear that at 12-week follow up, persistent ptosis ($3/7$) and motility restriction ($6/7$) were seen in the antibiotic alone group. (Keep in mind that motility restriction was defined as excursion of the eye measured in millimeters). The 14 patients receiving adjuvant corticosteroids did not have any residual ptosis or motility restriction. The authors did not elaborate on how the examiners were masked nor did they indicate whether diplopia accompanied the motility restriction, so there may have been bias.

I have never really thought about adding corticosteroids to the treatment of orbital cellulitis, but certainly our ENT colleagues do it a lot when they treat bacterial sinusitis. The thought behind reducing inflammation as we treat infection makes sense, and I think it deserves further exploration.

—Michael S. Lee, MD

This small study showed a more rapid recovery and mildly better outcome in orbital cellulitis patients who received corticosteroids after antibiotics were on board. Whether the benefit is related to anti-inflammatory effect or to a decrease in swelling in a tight "compartment" is not clear. Importantly, they report "no increase in steroid-related adverse events" although no details are provided. These results are consistent with findings in other bacterial infections, such as sepsis and meningitis, where corticosteroids are sometimes used.

—Mark L. Moster, MD
Invasive Thymoma in Ocular Myasthenia Gravis: Diagnostic and Prognostic Implications

We read with great interest the recent article by Bruce and Kupersmith (1) discussing the safety of prednisone in treating patients with ocular myasthenia gravis (OMG). Yet before treatment, there are critically important steps in evaluating these patients. We illustrate this point by presenting 2 cases of OMG that were found to have invasive thymoma.

Case 1: A 50-year-old Hispanic man presented with a 4-month history of ptosis and diplopia, which was worse in the evening and better in the morning. He had no other symptoms. Visual acuity was 20/20 bilaterally. External examination showed bilateral variable ptosis, which increased with sustained upgaze, mild orbicularis weakness, and positive Cogan lid twitch sign. The pupils were isocoric, and there was no relative afferent pupillary defect. Ocular motility revealed variable exotropia of 12–16 prism diopters and bilateral pseudointernuclear ophthalmoplegia. Ice test was positive, resulting in an improvement in ocular motility and ptosis. Ophthalmoscopy was normal bilaterally. Serum acetylcholine receptor antibodies were elevated: binding antibody = 33.0 nmol/L (positive, >0.5 nmol/L); blocking antibody = 48% (positive, >25%); modulating antibody = 44% (positive, >26%). Electromyographic and nerve conduction studies were diagnostic of myasthenia gravis. Computed tomography (CT) of the chest revealed a thymic mass (Fig. 1A).

At surgery, in addition to thymectomy, pericardial resection was performed because the tumor was found to be invading the pericardium. Pathology confirmed invasive thymoma, with mixed pattern grade B1, B2, and focal B3, and no lymphovascular or perineural invasion (stage III). Following surgery, the patient had near complete resolution of his myasthenic symptoms.

Case 2: A 67-year-old Caucasian woman developed left-sided ptosis and diplopia, and edrophonium testing and acetylcholine receptor antibodies were positive. CT of the chest disclosed nodular densities in the anterior mediastinum (Fig. 1B). Thymectomy revealed invasive thymic epithelial neoplasm with conventional and atypical features (stage II, grade B3). The patient received postoperative radiation therapy, and positron emission tomography (PET) and CT performed within the first year and a half the following surgery were negative for tumor recurrence or metastases.

Nineteen months after initial presentation, the patient developed an acute exacerbation of myasthenia gravis with ptosis, diplopia, shortness of breath, and upper extremity weakness. She had a complicated hospital course including atrial fibrillation and respiratory failure, and she was discharged 4 months later on weekly plasmapheresis, pyridostigmine, and prednisone. On examination, there was mild bilateral orbicularis weakness, but no Cogan lid twitch sign and variable exotropia of 20–50 prism-diopters and right hypertropia. Follow-up PET and chest CT have remained stable.

We emphasize 3 important points from our cases. First, it is essential that we remind our referring clinicians to obtain imaging of the mediastinum in patients with ocular and generalized myasthenia gravis (2,3). Second, delayed diagnosis and treatment of thymoma can lead to disease progression, a higher stage at diagnosis, and a worse systemic outcome as more invasive stages correlate with higher mortality rates (4,5). Third, patients who have undergone thymectomy for malignant or invasive disease and present...
with worsening myasthenic symptoms, including ocular complaints, might benefit from repeat mediastinal imaging to rule out recurrent or residual thymoma (6).

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Idiopathic Sclerosing Orbital Inflammation: Presentation of an Unusual Case With Isolated Bilateral Optic Nerve Involvement

We read with great interest the report by Levin et al (1) regarding the role of the optic nerve biopsy in the management of progressive optic neuropathy. We had the opportunity to evaluate a 50-year-old man with progressive deterioration of vision in his left eye for 2 months with minimal periorbital pain. Visual acuity was 20/20, right eye, and no light perception, left eye. The right fundus was normal but there was marked optic disc edema in the left eye (Fig. 1). Magnetic resonance imaging (MRI) of the brain and orbits demonstrated enhancement and thickening of the left optic nerve (Fig. 2). An extensive work-up including hematologic tests, lumbar puncture, and computed tomography of chest, abdomen, and pelvis was unremarkable. The patient was given 1 g of methylprednisolone intravenously for 3 days followed by a tapering dose of oral steroids over several months. Although there was improvement in the left optic disc edema, vision remained unchanged.

Four months after onset of symptoms, the patient reported vision loss in the right eye. Acuity was 20/40, right eye, and no light perception, left eye. Funduscopy revealed right optic disc edema and left optic atrophy. MRI demonstrated thickening of the right optic with marked enhancement following intravenous contrast. Prednisone was restarted at a dose of 1 mg/kg/d, and there was rapid improvement in the vision in the right eye with resolution of right optic disc edema.
Given involvement of the previously unaffected right eye, a biopsy of the left optic nerve was performed. Histopathology showed primarily fibrosis and an inflammatory infiltrate consisting of lymphocytes, histiocytes, and plasma cells (Fig. 3). No granulomas were identified. Stains for infectious, immune, and neoplastic disorders were nondiagnostic. Based on these results, a diagnosis of idiopathic sclerosing orbital inflammation (ISOI) was made.

ISOI is a rare condition characterized by marked fibrosis and some inflammatory infiltrate (2–4). However, unlike idiopathic orbital inflammation, which has an acute clinical onset, the progression of ISOI generally has a chronic and indolent course (5). In our patient, there was consecutive involvement of both optic nerves. There are reports of ISOI associated with systemic idiopathic fibrosis and increased serum levels of IgG4 (6,7). Our patient did not show increased serum levels of IgG4, and the biopsy specimen was negative for the presence of IgG4.

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REFERENCES

Intracranial Hypertension in a Patient Preparing for Gestational Surrogacy With Leuprolide Acetate and Estrogen

We read with great interest the editorial (1) and series of articles dealing with intracranial hypertension recently published in the Journal of Neuro-Ophthalmology. Gestational surrogacy, the process by which a genetically unrelated woman is implanted with an embryo, requires preparation with leuprolide acetate and estrogen. It is increasing as a management option for infertility. Intracranial hypertension is a rare adverse effect of sterility management with leuprolide acetate occurring after months or years of administration. We evaluated a 23-year-old multiparous woman being prepared for gestational surrogacy with injections, daily leuprolide acetate and twice weekly estrogen, who developed intracranial hypertension within 7 days of starting therapy. She developed gradual onset of holoccephalic pounding headache that increased in intensity over the course of 1 week and was made worse by maneuvers that increase intracranial pressure such as laying flat. She also had blurry vision and binocular horizontal diplopia. She had been on this regimen the previous year for gestational surrogacy and tolerated it well. She was not obese and her weight had been stable.

Visual acuity was 20/20, right eye, and 20/25, left eye, with normal color vision (Hardy–Rand–Ritter plates) and confrontation visual field testing. Extraocular movements demonstrated a right sixth nerve paresis, and funduscopy revealed bilateral optic disc swelling. Brain magnetic resonance imaging and MR venography were normal. Lumbar puncture was significant for an opening pressure of 440 mm Hg and a large volume of cerebrospinal fluid. Her headache improved immediately after the lumbar puncture and continued to improve following cessation of hormone therapy.

Leuprolide acetate is a synthetic gonadotrophin–releasing hormone or luteinizing hormone–releasing hormone analog used to treat sterility in women and prostate cancer in men (2). More recently, it has been used for gestational surrogacy. There are 2 reports describing intracranial hypertension in patients taking leuprolide, one in a patient on pulsatile pump for 2 years for sterility management and in another following discontinuation of the drug after 5 months of treatment (3,4). Fraunfelder and Edwards (5) suggested that cases in their review lacked sufficient data to determine whether intracranial hypertension was due to leuprolide.

In contrast, we documented intracranial hypertension occurring within 7 days of initiating treatment with leuprolide. The role of the two doses of estrogen she received and of previous treatment from previous gestational surrogacy is unclear. Although our patient was in the age group affected by idiopathic intracranial hypertension, she did not have associated comorbid conditions such as obesity or recent weight gain (6,7). Additionally, she improved rapidly with discontinuation of hormonal therapy suggesting that daily leuprolide likely induced the intracranial hypertension. Considering the increasing numbers of gestational surrogacy, the lack of similar case reports would imply that intracranial hypertension is a rare occurrence in this context. However, this diagnosis should be considered if a patient being prepared for surrogacy has new onset of headache, and a fundus examination should be performed to look for papilledema.

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Visual acuity was 20/20, right eye, and 20/25, left eye, with normal color vision (Hardy–Rand–Rittler plates) and confrontation visual field testing. Extraocular movements demonstrated a right sixth nerve paresis, and funduscopy revealed bilateral optic disc swelling. Brain magnetic resonance imaging and MR venography were normal. Lumbar puncture was significant for an opening pressure of 440 mm Hg following removal of 20 mL of cerebrospinal fluid. Her headache improved immediately after the lumbar puncture and continued to improve following cessation of hormone therapy.

Leuprolide acetate is a synthetic gonadotrophin-releasing hormone or luteinizing hormone-releasing hormone analog used to treat sterility in women and prostate cancer in men (2). More recently, it has been used for gestational surrogacy. There are 2 reports describing intracranial hypertension in patients taking leuprolide, one in a patient on pulsatile pump for 2 years for sterility management and in another following discontinuation of the drug after 5 months of treatment (3,4). Fraunfelder and Edwards (5) suggested that cases in their review lacked sufficient data to determine whether intracranial hypertension was due to leuprolide.

In contrast, we documented intracranial hypertension occurring within 7 days of initiating treatment with leuprolide. The role of the two doses of estrogen she received and of previous treatment from previous gestational surrogacy is unclear. Although our patient was in the age group affected by idiopathic intracranial hypertension, she did not have associated comorbid conditions such as obesity or recent weight gain (6,7). Additionally, she improved rapidly with discontinuation of hormonal therapy suggesting that daily leuprolide likely induced the intracranial hypertension. Considering the increasing numbers of gestational surrogacy, the lack of similar case reports would imply that intracranial hypertension is a rare occurrence in this context. However, this diagnosis should be considered if a patient being prepared for surrogacy has new onset of headache, and a fundus examination should be performed to look for papilledema.

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Pseudo-doubling of Optic Disc in a Case of Proliferative Diabetic Retinopathy

True optic disc duplication with 2 independent retinal vasculatures is rare (1). Lesions reported to simulate the optic disc include colobomas and inflammatory foci (2–4). We report a case of pseudo-optic disc doubling in a patient with proliferative diabetic retinopathy (PDR).

A 38-year-old man with advanced PDR and visual acuity of 20/400 in each eye was examined in our clinic. Fundus examination revealed retinal hemorrhages and fibrovascular proliferation over the optic disc and along the vascular arcades in both eyes. A disc-like structure was present along the superotemporal vascular arcade (Fig. 1). The media was hazy due to vitreous hemorrhage.

![FIG. 1. An optic disc-like structure is present along the superotemporal vascular arcade. The media is hazy due to vitreous hemorrhage.](image)

**Fig. 2.** A. Fluorescein angiogram (venous phase) shows that the blood vessels emerging from the pseudo-disc are actually continuation of those arising from the true optic disc. B. Fluorescein angiogram (late phase) demonstrates leakage from new vessels overlying both the true and pseudo-optic discs.
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Isolated Horizontal Gaze Palsy With Congenital Pontine Hypoplasia

We read with great interest the article by Connors et al. (1) published in the Journal on the “16 syndrome.” The authors described an interesting eye movement pattern characterized by bilateral limitation of horizontal eye movements and bilateral facial nerve palsies that was caused by an acquired disorder of the pontine tegmentum. We evaluated a patient with bilateral horizontal gaze palsies due to a congenital abnormality of the central nervous system.

An 11-year-old boy was referred to our clinic for evaluation of eye movements. Visual acuity was 20/20 in each eye. There was no abnormal head posture and the eyes were orthophoric in primary position. Ocular movements showed a bilateral horizontal gaze palsy with normal vertical eye movements. Horizontal movements could not be elicited with the Doll’s head maneuver and horizontal saccades and pursuit movements were absent. Convergence to a near target was normal (see Supplemental Digital Content, Video, http://links.lww.com/WNO/A76). Forced duction testing was negative and the remainder of the ocular examination was unremarkable.

Brain magnetic resonance imaging (MRI) revealed hypoplasia of the dorsal pons with a midsagittal cleft extending ventrally from the floor of the fourth ventricle (Fig. 1). The facial colliculi were absent and there was mild atrophy of the midbrain and medulla.

REFERENCES
present along the superotemporal arcade of the left eye, which was yellow in color with ill-defined margins (Fig. 1). Fluorescein angiography showed that the blood vessels emerging from the pseudo-disc were actually continuation of vessels from the true optic disc and demonstrated early hyperfluorescence (Fig. 2A) followed by late leakage (Fig. 2B). Optical coherence tomography (OCT) through the lesion showed an irregular thick hyper-reflective membrane over the retina continuous with fibrovascular proliferation (Fig. 3). The subretinal yellow exudates, circular fibrovascular proliferation with new vessels emerging centrifugally gave the appearance of an optic disc. But absence of an independent vasculature on fluorescein angiography (5) and the lack of a crater-like depression on OCT confirmed the lesion to be pseudo-optic disc. We are unaware of the previous reports of pseudo-optic disc doubling due to proliferative diabetic retinopathy.

The authors report no conflicts of interest.

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Brain magnetic resonance imaging (MRI) revealed hypoplasia of the dorsalpons with a mid sagittal cleft extending ventrally from the floor of the fourth ventricle (Fig. 1). The facial colliculi were absent and there was mild atrophy of the midbrain and medulla.
A variety of congenital disorders of the pons have been reported with horizontal gaze palsy. These include Moebius syndrome (2), associated with synergetic convergence (3) and with scoliosis (4,5). The clinical findings of scoliosis appear to require atrophy of the medulla (“butterfly” configuration on MRI), which was not present in our case.

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Parenchymal Anaplastic Astrocytoma Presenting With Visual Symptoms Due to Bilateral Optic Nerve Sheath Involvement

We read with interest the recent report by Traynis et al (1) regarding gliomatosis cerebri presenting with anterior visual pathway involvement. We evaluated a patient that further expands the neuro-ophthalmic spectrum of central nervous system gliomas. A 23-year-old man reported bilateral, transient visual obscurations. Examination revealed normal visual acuity, mild blind spot enlargement on visual field testing, and bilateral optic disc edema. Magnetic resonance imaging (MRI) of the brain demonstrated a left thalamic lesion with increased T2 signal and no enhancement. Multiple MRIs during the next 5 months were stable. Five and a half months after presentation, the visual obscurations became more frequent and the patient developed bilateral peripheral visual field loss. He denied headache and fever, and medical history, social history, and family history were unremarkable.

FIG. 1. A. T2 axial magnetic resonance imaging (MRI) demonstrates a midsagittal cleft (arrow) producing “split pons sign.” B. T1 sagittal MRI shows pontine hypoplasia with abnormal appearance of the floor of the fourth ventricle.

REFERENCES


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When we first examined the patient, visual acuity was 20/50, right eye, and 20/200, left eye. Visual fields were constricted bilaterally and there was marked optic disc edema with subretinal fluid extending into the macula in each eye. Ophthalmic and neurological examinations were normal otherwise.

Two lumbar punctures had opening pressures of 23 and 22 cm of water. Cerebrospinal fluid (CSF) had 13 white blood cells/μL with monocytic predominance, 46 mg/dL protein, and normal or negative testing for glucose, bacterial culture, venereal disease research laboratory, oligoclonal bands, angiotensin-converting enzyme (ACE), and malignant cells. CSF cytology from a third lumbar puncture revealed rare spindle cells with mild atypia.

Hematologic tests, including antinuclear antibody, aquaporin 4 antibody, and ACE levels, were within normal limits as were studies for Lyme disease, coxsackie virus, varicella-zoster virus, arbovirus, West Nile virus, Bartonella henselae, syphilis, Cryptococcus neoformans, toxoplasmosis, Coccidioides, and HIV.

Brain MRI demonstrated a stable, nonenhancing left thalamic mass (Fig. 1). Magnetic resonance (MR) spectroscopy showed decreased N-acetylaspartate resonance signal intensity and increased signal intensity, consistent with a low-grade neoplasm or inflammatory process. Orbital MRI showed increased fluid space and enlargement of the optic nerve sheaths (Fig. 2). Brain MR angiography and venography and spine MRI were within normal limits as were computed tomography of the chest, abdomen, and pelvis and a gallium scan.

Despite empiric treatment with systemic corticosteroids, visual function worsened. Stereotactic biopsy of the thalamic lesion and left frontal meninges revealed parenchymal anaplastic astrocytoma, World Health Organization (WHO) grade III, in thalamic tissue samples and findings suggestive of leptomeningeal spread of glioma (Fig. 3). Immunohistochemistry studies showed that tumor cells were positive for glial fibrillary acidic protein (GFAP) and negative for leukocyte common antigen, CD68, CD3, and CD20. Many cells stained with p53, consistent with the presence of p53 mutation in tumor cells. The Ki-67 proliferation marker stained more than 5% of tumor cells, and the leptomeningeal sample demonstrated focal staining of a low number of cells with GFAP, p53, and Ki-67. Optic nerve sheath biopsy (Fig. 3C) was not diagnostic of tumor spread or another process.

The patient was treated for 6 weeks with concurrent temozolomide (75 mg/m² daily) and whole brain radiation of 45 Gy in 1.8 Gy fractions and then placed on...
maintenance chemotherapy with temozolomide (200 mg/m² daily for 5 days every 28 days for a planned total of 6 cycles).

Visual acuity stabilized at hand motion in the right eye and light perception in the left eye with some expansion of the right eye visual field. Ophthalmoscopic examination showed bilateral optic disc pallor. MRI of the brain and orbits revealed slight interval decrease in size of the thalamic tumor, reduction in mass effect on the third ventricle, and enhancement of both optic nerves. The patient developed left buttock pain, and MRI showed new leptomeningeal enhancement within the thoracic spine suggestive of further tumor spread.

Our patient had a parenchymal anaplastic astrocytoma and presented with transient visual obscurations due to presumed neoplastic spread to the optic nerve sheaths. Although we do not have pathological confirmation of leptomeningeal spread, the findings of the optic nerve sheath biopsy, CSF analysis, and clinical course provide supportive evidence.

Leptomeningeal spread of malignant astrocytomas is well described. In a study of patients with high-grade gliomas (33 anaplastic astrocytoma and 35 glioblastoma multiforme) reported by Saito et al (2), 25% had intracranial dissemination and 6 (9%) had spinal dissemination. All those with spinal dissemination had primary thalamic or temporal lobe tumors and the authors proposed proximity to CSF circulation as a risk factor for dissemination. In a case series of postmortem confirmed cases of leptomeningeal infiltration, Boyle et al (3) found that 18 of 63 cases were associated with an intracranial mass lesion and 7 of these were astrocytomas. Of the 18 cases associated with an intracranial mass lesion, CSF contained malignant cells in only 21%, and presenting signs included optic disc edema in 45%. The authors proposed that papilledema may have represented either elevated intracranial pressure or neoplastic optic nerve infiltration but did not have sufficient clinical data to make this distinction. In our patient, elevated intracranial pressure was excluded by serial lumbar punctures.

In our patient, the nonenhancing appearance of the thalamic mass on MRI and its stability on serial scans led to the initial diagnostic consideration of a low-grade neoplasm unrelated to his neuro-ophthalmic symptoms and signs. Several case series reinforce that neuroimaging characteristics do not reliably predict histological grade. In both retrospective and prospective studies of parenchymal brain lesions without enhancement, between 35% and 45% are WHO grade III on histological examination (4,5). One study estimated that 9% of malignant supratentorial gliomas lack contrast enhancement (6). It has been suggested that advanced imaging modalities, such as perfusion-weighted imaging and MR spectroscopy, may provide additional insight into the malignant potential of intracranial lesions (7–9). Yet as our case illustrates, false-negative results limit the utility of these techniques. One possible reason for imaging and histological discrepancy might be heterogeneity within the tumor with focal high-grade transformation (10).

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Linezolid-Associated Optic Neuropathy in a Patient With Drug-Resistant Tuberculosis

We enjoyed reading the review article by Wang and Sadun (1) dealing with drug-induced mitochondrial optic neuropathies. Recently, we evaluated a patient taking linezolid, a synthetic antimicrobial agent effective against gram-positive bacteria, including vancomycin-resistant enterococci and methicillin-resistant staphylococci as well as drug-resistant strains of Mycobacterium tuberculosis (2,3). This antibiotic has been linked to optic neuropathy (4–11). Our patient’s presentation appears unusual in that it was not associated with prominent optic disc swelling.

A 41-year-old woman was referred for evaluation of visual function. She had a history of pulmonary tuberculosis and had been treated with linezolid for 17 months. Initial visual acuity was 20/20, right eye and 20/20, left eye. No abnormalities were detected in the examination of the

**FIG. 1.** (A) Twenty months after beginning linezolid, automated visual fields demonstrate subtle field loss in the right eye and reduced sensitivity in the left eye. (B) Two months after linezolid was discontinued, visual fields show improvement bilaterally.
Linezolid-Associated Optic Neuropathy in a Patient With Drug-Resistant Tuberculosis

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A 41-year-old woman was referred for evaluation of visual function. She had a history of pulmonary tuberculosis and had been treated with linezolid for 17 months. Initial visual acuity was 20/20, right eye and 20/20, left eye. No abnormalities were detected in the examination of the suspected adult supratentorial (low-grade) astrocytoma.


FIG. 1. (A) Twenty months after beginning linezolid, automated visual fields demonstrate subtle field loss in the right eye and reduced sensitivity in the left eye. (B) Two months after linezolid was discontinued, visual fields show improvement bilaterally.
anterior segment of each eye and the fundi. Visual fields were normal. Additional medications included cycloserine, prothionamide, and p-aminosalicylic calcium.

Three months later, the patient complained of visual impairment and tingling in both legs. Visual acuity was 20/30, right eye and 20/40, left eye. Pupillary reactions were normal but color vision was reduced bilaterally. Results of visual field testing are shown in Figure 1A and funduscop[y demonstrated mild temporal disc pallor in each eye (Fig. 2). Optical coherence tomography (OCT) revealed an increase in retinal nerve fiber layer (RNFL) thickness in the inferotemporal quadrant of each eye (Fig. 3A).

Linezolid was stopped, and the patient continued on cycloserine, prothionamide, and p-aminosalicylic calcium. Two months later, visual acuity improved to 20/20 in both eyes with intact color vision. Visual fields returned to near normal (Fig. 1B) and the optic discs were unchanged. The inferotemporal RNFL was no longer thickened on OCT (Fig. 3B). Eight months later, visual function was stable, but the patient reported persistent tingling in both legs.

Linezolid is part of the oxazolidinone class of antibiotics that inhibit bacterial protein synthesis by binding to the 70S ribosomal initiation complex (12). Although this complex is not present in mammalian cells, it has been shown to reduce mitochondrial respiratory chain enzyme activity in experimental animals and in a patient receiving linezolid therapy who developed optic neuropathy (13). Although the precise mechanism for linezolid-induced optic neuropathy is unknown, impairment of mitochondrial function within retinal ganglion cells is likely (9,14).

An interesting OCT finding in our case was the increase of RNFL thickness in the temporal and inferior quadrants without visible optic disc swelling. A similar alteration of RNFL was described by Barboni et al (15) in Leber hereditary optic neuropathy (LHON). Since LHON is known to be associated with mitochondrial dysfunction, the similarity in RNFL changes in the 2 disorders further

FIG. 2. There is temporal pallor of both optic discs.

FIG. 3. Optical coherence tomography. A. Initially, there is swelling of the inferotemporal RNFL in both eyes. B. Two months after discontinuation of linezolid, swelling of the inferotemporal RNFL has resolved.
links linezolid-induced optic neuropathy to a disturbance in mitochondrial energy production (16).

The occurrence of linezolid optic neuropathy may be associated with the duration of therapy. Although recommended treatment is for 28 days, linezolid often is given for longer periods of time in patients with high risk or resistant bacterial infections (7–11,14). Such was the case in our patient. However, there are exceptions. Joshi et al (17) described optic neuropathy occurring 16 days after beginning linezolid in a patient with acute lymphocytic leukemia.

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The Founding of the International Neuro-Ophthalmology Society

Michael D. Sanders, FRCP, FRCS, HonFRCOphth, H. Stanley Thompson, MD

The first formal international meeting of neuro-ophthalmologists took place in April 1976 in the ancient chateau of La Napoule in the south of France (Fig. 1).

The multidisciplinary acorn planted at this meeting has grown into a sturdy oak that encompasses all of the medical and neurological aspects of the visual sensory and ocular motor systems. Initially, neuro-ophthalmology was a clinical subspecialty that entertained a few ophthalmologists, those with a medical orientation, and some neurologists interested in visual examination for cerebral diagnosis. Subsequently, it has expanded dramatically. Major advances in the anatomy and particularly in the physiology of the visual and ocular motor systems, combined with dazzling improvements in neuroimaging, have created a vigorous subspecialty. There are now many active neuro-ophthalmology training programs in clinics and teaching hospitals around the world and several organizations that encourage progress in neuro-ophthalmology both in peer-reviewed journals and in national and international societies.

It was a chance breakfast meeting at the annual meeting of the American Academy of Ophthalmology in 1974, between Tom Hedges of Philadelphia and Freddie Huber of Zürich (Fig. 2), that sowed the seeds for an international meeting of neuro-ophthalmologists.

Tom Hedges had been a fellow with Frank B. Walsh at the Johns Hopkins Hospital in Baltimore, before becoming Professor of Ophthalmology at the University of Pennsylvania, with an interest in neuro-ophthalmology. Freddie Huber had also been interested in the subject and worked closely with Professor Hugo Krayenbühl, the distinguished neurosurgeon in Zürich. Hedges and Huber sensed that it was about time for specialists in neuro-ophthalmology to start thinking about opportunities for international communication, consolidation, and progress.

It was in January 1975 that the University of Pennsylvania became the Trustee of the Chateau of La Napoule. The University wanted to use the facility for meetings because of its attractive position on the coast in the south of France. Tom Hedges saw it as an ideal location for an international gathering of neuro-ophthalmologists.

The Chateau originally was built in the 14th century by the Villeneuve family. Over the centuries, it had served as a fortress, a monastery, a castle, and a seaport and in the 19th century as a glass factory. The chateau has been besieged in turn by the Saracens, the Romans, the Spaniards, the English, and the Germans and has been destroyed and rebuilt eight times.

At the end of the First World War, the chateau was liberated by the American Fleet, and soon thereafter, it was purchased by an artistic American couple, Henry and Marie Clews, who could afford to restore and decorate it in their own special style.

The Clews family had left their pottery business in England and settled in Ohio in 1838, where they continued their craft. A member of the Clews family settled in New York and was able to establish a successful Wall Street firm. It was his son, Henry Clews (1876–1937), an artist, sculptor, and poet, who bought the Chateau in 1918.

Clews and his wife Marie (Fig. 3) set about rebuilding the chateau, creating their romantic home, their idyll, and their life. She did the gardens, and he did the stonework (1) (Fig 4).

The Clews Foundation was created in 1951 by Marie Clews in memory of her husband. Marie Clews died in 1959, and their Foundation still supports the chateau, to foster international and interdisciplinary exchange, and as a museum of the couples’ art and creativity. Many of Henry Clews’ highly prized sculptures can still be seen at La Napoule, and their quality and eccentricity are well demonstrated in Venneman’s crisp images (2).

The Growth of Neuro-Ophthalmology

Physicians and scientists in the 17th and 18th centuries were interested in properties of light and in the nature of vision, but the 19th century saw an explosion in knowledge that led to the development of compound lenses and the invention of the ophthalmoscope by Helmholtz in 1851.

In the late 19th century, American neuro-ophthalmology stood on the shoulders of European neurologists and ophthalmologists. Then in the 20th century, many full-time American neuro-ophthalmologists devoted their time to clinical practice, teaching, and publishing. They trained interested students from America, Europe, and eventually the rest of the world. The leaders of this movement included Frank B. Walsh at the Johns Hopkins Hospital in Baltimore,
David C. Cogan in Boston, and William F. Hoyt at the University of California, San Francisco. The group in Miami led by J. Lawton Smith became known for their skill, their enthusiasm, and their vigorous sense of humor. The neuro-ophthalmologists trained at these institutions introduced neuro-ophthalmology as a recognized subspecialty of both neurology and ophthalmology.

Organizing the meeting at La Napoule in 1975 saw extensive transatlantic correspondence about participants and the inclusion of neurologists, neurosurgeons, and radiologists. The number of attendees was limited to 50 (Fig. 5), the registration fee was $70, and the joint presidents were Tom Hedges and Freddie Huber.

FRANK B. WALSH

The Guest of Honor was Frank B. Walsh who was brought by his previous fellow, Adolphe Neetens, from Belgium to the south of France by car. Dr Walsh made the trip from Baltimore on the condition that he could arrange to visit the grave of his son, who was killed in Holland in the Second World War. Frank B. Walsh was a delightful avuncular Canadian, who trained in Manitoba and after 7 years in general practice, and at the age of 35, began a residency in ophthalmology at the Johns Hopkins Hospital with Dr Wilmer. Progressing to the Consultant Staff, he joined his brilliant and energetic colleagues in neurosurgery, Walter Dandy, and in pediatric neurology, Frank Ford.

Frank B. Walsh produced the first edition of his classic textbook, "Clinical Neuro-Ophthalmology," in 1947. It was this book (enlarged later by his students Hoyt and then Miller, and then Nancy Newman, in 1998, to five volumes and almost 6,000 pages) that showed the world how much was included in this subspecialty. It was this pioneering book, combined with his teaching and his charisma, that earned Walsh the approbation of colleagues and the mantle of "Doyen of Neuro-Ophthalmology."

The first meeting of what was to become the International Neuro-Ophthalmology Society (INOS) was held in 1976 in the hall of the Chateau de la Napoule, surrounded by Clews’ sculptures. The moderators of the various sessions were:
1. Frank B. Walsh (United States) and Alfred Huber (Switzerland)
2. Thomas R. Hedges (United States) and Adolphe Neetens (Belgium)
3. Michael Sanders (United Kingdom) and Guy Offret (France)
4. Mark Mishkin (United States) and Arno Nover (Germany)
5. Melvin Alper (United States) and Stan Thompson (United States)
6. Paul Bregeat (France) and Noble David (United States)
7. Fred Simeone (United States) and Donald Smith (United States)
8. L. Guillaumat (France) and Guntram Kommerell (Germany)
9. Joel Glaser (United States) and Lars Frisen (Sweden)
10. Dieter Schmidt (Germany) and Henry Van Dyke (United States)
11. Trevor Kirkham (United Kingdom) and Nancy Newman (United States).

The majority of papers at the meeting were by ophthalmologists, though four were by neurosurgeons and two each by neurologists, pediatric ophthalmologists, and neuropathologists. Frank B. Walsh gave a paper on his experiences with the meningiomas of childhood, and the main clinical theme was the advent of computed tomography with presentations by Alper, Bregeat, Moseley, Sanders, and Trokel. Gastro-nomic standards for future meetings were set at the highest possible level by the generosity of the Mayor of La Napoule who took us to a 2-star Michelin restaurant, called “Oasis.” Pink champagne was followed by 6 delicate courses.
The first Council Meeting established the “International Neuro-Ophthalmology Society,” elected officers, and laid down the principle that the incoming President would organize the subsequent meeting and that costs would be kept to a minimum. The incoming president was Mel Alper from Georgetown University in Washington, DC, with the intention of holding the next meeting at an American location.

**INOS 1978–2012**

The Council decided that in order to attract new material, meetings of the society should be held biennially, with venues alternating between the United States and Europe. After 10 years, a meeting was held in Hakone, Japan, under the stewardship of Satoshi Ishikawa in response to the great interest in neuro-ophthalmology in that country. Combined meetings with other societies first occurred in 1980 when David Knox brought the Frank B. Walsh Society to the meeting in Valbella under the presidency of Freddie Huber.

In 1988, Bob Hepler and Stan Thompson staged a combined meeting of all groups interested in neuro-ophthalmology. At this meeting, INOS, the International Perimetric Society, the Clinical Eye Movement Society, the Rocky Mountain Neuro-Ophthalmology Society, and the Frank B. Walsh Society all met in Vancouver, Canada. This was a great success, demonstrating the breadth of neuro-ophthalmology, but some smaller societies did feel a bit marginalized.

All INOS presidents have been ophthalmologists, with the exception of two neurologists, Michael Halmagyi from Australia and James Sharpe from Canada. The presidents realized the extra organizational burden involved in setting up a “one-off” meeting. Only two people have organized multiple meetings: Freddie Huber (1976, 1980) and Neil Miller (1982, 1992, 2008).

Guests of Honor have included Frank B. Walsh (1976), David Cogan (1982), and William F. Hoyt (1990). INOS meetings subsequently have taken place every two years and spread over most parts of the globe (Table 1). Those countries interested in neuro-ophthalmology have received full support of the international community. And that community owes a tremendous debt of gratitude to the visionary efforts of Tom Hedges and Alfred Huber.

**REFERENCES**


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<th>Date</th>
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<td>2002</td>
<td>Argentina—Buenos Aires</td>
<td>Roberto Ebner</td>
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<td>2004</td>
<td>Switzerland—Geneva</td>
<td>Avinoam Safran</td>
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<td>2006</td>
<td>Japan—Tokyo</td>
<td>Masato Wakakura</td>
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<tr>
<td>2010</td>
<td>France—Lyon</td>
<td>Alain Vighetto, Caroline Tilikete</td>
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<td>2012</td>
<td>Singapore</td>
<td>Kong Yong Goh, Sharon Tow</td>
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Neuro-Ophthalmology in Israel

Ruth Huna-Baron, MD, Eitan Zvi Rath, MD

Neuro-ophthalmology was introduced in Israel during the late 1970s by Riri Manor, Yochanan Goldhammer, and Isaac Gutman (Fig. 1). They trained with from William Hoyt, Lawton Smith, and Myles Behrens, respectively. These pioneers trained many local ophthalmologists, neurologists, and neuro-ophthalmologists in Israel, and their efforts resulted in 21 neuro-ophthalmologists currently serving a population of 8 million. Many Israeli neuro-ophthalmologists did fellowships in the United States with a variety of other mentors, including Ronald Burde, Joel Glaser and Norman Schatz, Mark Kupersmith, Byron Lam, Neil Miller, Barry Scarf, and Jonathan Trobe.

In Israel, each citizen is entitled to health care services under the National Health Insurance Law. To meet the challenge of the rapid development of new and expensive diagnostic and therapeutic modalities, a committee of the Ministry of Health each year announces new technologies and therapies to be included in basic health coverage. There are 18 magnetic resonance imaging devices in Israel and 5 interventional neurovascular units, and most medical centers in the country have a neuro-ophthalmology service (Table 1). Much like in the United States, referrals come from neurologists, ophthalmologists, neurosurgeons interventional neuroradiologists, and endocrinologists.

In 1997, the Israeli Neuro-Ophthalmology Society was founded by Riri Manor as a subspecialty section of the Israeli Ophthalmology Society. Two annual meetings are organized by the society, of which one hosts a leading...
TABLE 2. Neuro-ophthalmic research in Israel

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<tr>
<td>1</td>
<td>Idiopathic intracranial hypertension: pediatric, thrombophilic factors</td>
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<td>2</td>
<td>NAION: C-reactive protein, experimental model</td>
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<td>3</td>
<td>Thyroid eye disease: dysthyroid optic neuropathy</td>
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<td>4</td>
<td>OCT in: Parkinson disease, minor cognitive impairment, Alzheimer disease, NAION</td>
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<td>Stem cells: glial and neuronal markers</td>
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<td>Meningioma—surgical and radiation outcomes</td>
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<td>Functional MRI: optic neuritis</td>
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<td>8</td>
<td>Multiple sclerosis: gene expression</td>
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MRI, magnetic resonance imaging; NAION, nonarteritic anterior ischemic optic neuropathy; OCT, optical coherence tomography.


Every other year, the Israeli Ophthalmological Society meeting features neuro-ophthalmology. Also, among the 4 sessions of the Israeli Ophthalmology Board examinations, 1 is dedicated to neuro-ophthalmology and oculoplastics surgery.

Internally, the Israeli Ophthalmological Society is involved in basic and clinical research (Table 2). There also are multicenter studies under way, such as the phase 1 trial of intravitreal injection of QPI-1007 in NAION. Nitza Cohen-Goldenberg received a North American Neuro-Ophthalmology Society (NANOS) Pilot Research Grant in 2008.

Members of the Israeli neuro-ophthalmology community are active in international societies, including NANOS and European Neuro-Ophthalmological Society (EUNOS). In 1999, the EUNOS meeting was held in Jerusalem. Neuro-ophthalmic publications from Israel appear in leading ophthalmology and neurology journals. Two fellows from Israel currently are training in neuro-ophthalmology, and the future here appears bright for our subspecialty.

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ADDENDUM

The February, 2013 issue of Halefuah – The Journal of the Israel Medical Association - was devoted to neuro-ophthalmology. Anat Kesler served as guest editor & a wide range of topics were covered including neuromyelitis optica, ischemic optic neuropathies and an update on idiopathic intracranial hypertension. This particular issue of the journal was entitled: “Neuro-Ophthalmology: the eye as a window to the brain.”
Interest in neuro-ophthalmology in France dates back to the 19th century with the publications by an ophthalmologist, Henri Parinaud, a collaborator of Jean-Martin Charcot in Paris. At that time, a physiologist, Claude Bernard, and a neurologist, Eugène Devic, participated in the description of various neuro-ophthalmologic syndromes. In the 1930s, academic neurologists in Paris, including Pierre Mollaret, Georges Guillaum and later Jérôme Garcin, Jean Lapresle, and Mongi Ben Hamida, worked closely with specific ophthalmologists, like Hoang Xuan Man, and published original clinical cases related to neuro-ophthalmology.

In the 1970s, neuro-ophthalmology emerged as a distinct subspecialty practiced by a few nonsurgical ophthalmologists, like Monique Schaison-Cusin, who saw patients in the neurology and neurosurgery departments of Pitié Salpêtrière Hospital in Paris. With reform of residency training in the early 1980s, ophthalmology primarily became a surgically oriented specialty and trainees lost the opportunity to choose ophthalmology as a medical specialty, thereby precluding training in neuro-ophthalmology. This led the last generations of French ophthalmologists to have little interest in neuro-ophthalmology, yet at the same time a number of investigators became interested in eye movement disorders. These included Pierre Larmande, Charles Pierrot-Deseilligny, Alain Berthoz, and Marc Jeannerod. They developed eye movement laboratories that attracted a number of neurologists and scientists over the past few decades.

French neuro-ophthalmology is usually performed part-time either by ophthalmologists or neurologists or in some locations by combined teams. Approximately, 30 clinicians currently practice neuro-ophthalmology on a regular basis in France. Two thirds of them are ophthalmologists, and most are located in academic medical centers.

Three major factors have led to a dramatic increase in educational, clinical, and research activity in neuro-ophthalmology in France. First was the creation 15 years ago of a post-graduate university diploma in neuro-ophthalmology. Since then, the registration has remained full each year (60 trainees). This program spurred creation of a French textbook of neuro-ophthalmology (1). Currently, neuro-ophthalmology is included in the educational programs of ophthalmology residents and is expected to be part of the curriculum of neurology residents very soon. A number of organizations provide grant support for neuro-ophthalmology training and include Berthe Fouassier Price [Fondation de France], Société Française d’Ophtalmologie, Année recherche; Institut Servier, Fondation Planiol, Fondation Philips. These grants allow young French ophthalmologists or neurologists to train in neuro-ophthalmology centers outside of France, primarily in the United States and United Kingdom.

FIG. 1. Number of participants and location of annual meeting of Club Francophone de Neuro-Ophthalologie.
Second, in 2003, the “Club de Neuro-Ophtalmologie Francophone” (CNOF) was established. This organization allows all clinicians interested in neuro-ophthalmology in France and French-speaking countries (Switzerland, Belgium, and for the 2014 meeting, Morocco) to share material related to clinical care, research, and education. Since its creation, the CNOF has successfully organized 3 national meetings every year, including 1 specific event and 2 events included within those, the French Society of Neurology (JNFL) and the French Society of Ophthalmology (SFO) meetings. Following the 2004 meeting of the French Society of Ophthalmology, a French textbook on neuro-ophthalmology was published (2). Three collaborative research projects have emerged from the CNOF: a survey of idiopathic intracranial hypertension in France (3); a multicenter study of recurrent optic neuritis to be published soon; and a survey of the incidence of optic neuritis in France. Recently, a website (http://www.neuro-ophtalmologie-club.org) was launched. The annual CNOF meeting takes place in different cities (Fig. 1), and the steady increase of the number of participants reflects the growing interest in neuro-ophthalmology. CNOF offers 2 travel grants a year for young investigators to allow them to attend international neuro-ophthalmology meetings.

Third, neuro-ophthalmology in France has developed an international focus. An increasing number of ophthalmologists and neurologists have been trained in the United Kingdom and the United States over the past 20 years, allowing for international collaborative projects, multiple international publications, and participations in international clinical, research, and educational meetings. In 2010, a very successful meeting of the International Neuro-Ophthalmology was held in Lyon.

Neuro-ophthalmology in France has made great strides in recent years. We are excited about an even brighter future!

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REFERENCES

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