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BOOKS RECEIVED

E8 Acknowledgment of Reviewers: 2014
The Editor and Editorial Board of the Journal of Neuro-Ophthalmology gratefully acknowledge the many reviewers who contributed their valuable time for the Journal this year. A list of 2014 reviewers appears in the online version of this issue, at www.jneuro-ophthalmology.com.
Fellowship training in neuro-ophthalmology in the United States has slowly been evolving. Initially, fellowship programs across all of ophthalmology, including neuro-ophthalmology, were highly variable in quality and content and were not subject to external oversight, standardization, or regulation. Historically, an analogous lack of accreditation and standardization was a problem for residency training in ophthalmology as well. Since 1981, the Accreditation Council for Graduate Medical Education (ACGME) has accredited residency training in ophthalmology and recently 1 subspecialty fellowship area, orbit and oculoplastic surgery. Currently, there are 5 ACGME-approved orbit/oculoplastic fellowship programs. The ACGME does not accredit other subspecialty fellowships in ophthalmology including neuro-ophthalmology. Instead, neuro-ophthalmology fellowships follow the requirements developed by the Association of University Professors in Ophthalmology (AUPO) Fellowship Compliance Committee (FCC) and the North American Neuro-Ophthalmology Society (NANOS). The AUPO decided to develop a compliance process rather than following the ACGME requirements because of cost and administrative complexities. The AUPO FCC Limited Liability Corporation document was signed by Bartly Mondino, MD, Executive Vice President of the AUPO, on March 23, 2005. NANOS decided to use the AUPO FCC process to allow neuro-ophthalmology fellowship education to occur in both Ophthalmology and Neurology departments. The stated goals and objectives of the AUPO FCC are to provide a system that would enhance patient care for ophthalmologic diseases by promoting uniform standards for fellowship training and educational programs in the ophthalmic subspecialties (Cornea, External Disease, and Refractive Surgery; Glaucoma; Neuro-Ophthalmology; Oncology/Pathology; Pediatric Ophthalmology and Strabismus; Surgical Retina and Vitreous; and Uveitis).

There are 19 voting members in the AUPO FCC with 6 pairs of representatives from the respective participating subspecialties (Cornea, Glaucoma, Neuro-Ophthalmology, Oncology/Pathology, Pediatric Ophthalmology and Strabismus, and Uveitis); 3 representatives from Surgical Retina and Vitreous (because they have 3 participating subspecialty societies); and 4 members from the AUPO. There also are 2 nonvoting advisors. The current neuro-ophthalmology representatives to the AUPO FCC process are A. G. Lee, MD, and A. Arnold, MD. J. L. Keltner, MD, as the founding chair of the AUPO FCC, will retire from this position and be replaced as chair by Michael Belin, MD, on March 1, 2015.

Although the AUPO FCC compliance process is entirely voluntary, many national subspecialty organizations, including NANOS, strongly encourage, endorse, and support the AUPO process for neuro-ophthalmology fellowship programs. Each subspecialty, including neuro-ophthalmology, through the action of their subspecialty education committee (i.e., the NANOS Professional Standards Fellowship Committee) participates in all aspects of the graduate medical educational process for compliance. The Professional Standards Fellowship Committee along with the AUPO FCC developed a set of standard requirements for neuro-ophthalmology fellowship subspecialty training (including the curriculum requirements, qualifications for faculty and fellows participation in research and clinical experience). In addition to the subspecialty-specific process, the AUPO FCC also has developed general subspecialty requirements applicable to all ophthalmology fellowships in the United States.
The AUPO FCC determines the suitability of initial program applications. Programs admitted to the AUPO FCC compliance program are monitored on a triennial or quadrennial review basis to insure compliance (Table 1). All neuro-ophthalmology fellowship programs in compliance with the AUPO FCC are listed at the AUPO FCC Website at www.aupofcc.org. Although not all of the current neuro-ophthalmology programs in the United States participate in the AUPO FCC process, the majority of programs do and it is hoped that one day, all programs will participate. Some subspecialty organizations require completion of an AUPO FCC approved fellowship program to become a fellow in the subspeciality society, but NANOS has not chosen to pursue this requirement at this time. There are currently 19 AUPO FCC compliant fellowship programs in neuro-ophthalmology in the United States, and the full list of compliant programs can be accessed at http://www.aupofcc.org/programs_in_compliance.html?specialty=neuro.

In addition to the AUPO FCC process, a centralized application service for fellowship applicants is available through the San Francisco (SF) Match for all ophthalmology fellowship subspecialties except for Neuro-Ophthalmology and Pathology who do not participate in the process. Therefore, applicants applying for Neuro-Ophthalmology must interview, compete for, and ultimately accept or decline individual offers from fellowship programs without the match process. The reasons for neuro-ophthalmology not participating in the SF Match are complex. The Professional Standards Fellowship Committee of NANOS revisits this question annually and surveys the fellowship program directors to gauge interest in participating in the SF Match.

Ultimately, the role of the AUPO FCC is to monitor educational standards, to protect the public, institutions, and trainees, and to provide an infrastructure for accountability and enforcement. The AUPO, the parent organization with responsibility for planning, promoting, and delivering graduate medical education in ophthalmology, provides oversight to the AUPO FCC, but our specialty organization, NANOS, provides input, representatives, and direct communication to the AUPO FCC.

The NANOS Professional Standards Committee (a Fellowship Education Committee is a requirement to participate in the AUPO FCC) meets at the annual NANOS meeting. At that meeting, the AUPO FCC standards and requirements for neuro-ophthalmology fellowship training are discussed, and revisions are made and approved as needed. The committee discusses the ongoing issues of participation or nonparticipation in the SF Match and other questions related to the AUPO FCC process and professional standards.

Now that there are 19 AUPO FCC compliant fellowship programs in neuro-ophthalmology in the United States, 2 major issues will have to be dealt with by the NANOS Board of Directors: 1) Is it fair and appropriate for fellowship applicants to continue not to have NANOS participate in some type of formal matching process? 2) In the future, should full fellows in NANOS be required to be trained only by programs that are AUPO FCC compliant? These are difficult questions that merit continued discussion and debate.

We have had very positive feedback on the AUPO FCC process from participating fellows (through fellow exit surveys) and participating programs. We believe that the standardization and oversight offered by the AUPO FCC has improved graduate medical education in neuro-ophthalmology and has provided the intended protection for the trainees, the programs, and most importantly the patients.

We are delighted that this editorial is being published in March 2015, exactly 10 years since formal implementation of the AUPO FCC process!

### Table 1. Objectives of the AUPO FCC process

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<th>Objective</th>
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<td>The AUPO FCC will establish a format and standard requirements for each subspecialty participating in the AUPO FCC process. The AUPO FCC will make determinations of the compliance of initial applications of individual fellowship programs for inclusion in the compliance program. Programs admitted to the compliance program will be monitored on a triennial or quadrennial program review basis to assure that they remain in compliance. Application and compliance monitoring will be accomplished through a web-based system. Compliance status will be made publicly available so that fellowship applicants may use this information in their decision. Likewise, mentors will have compliance status available when advising residents on fellowship opportunities. It is also worth noting that this year surgical statistics for the following subspecialties are now posted on the AUPO FCC Website: Pediatric Ophthalmology &amp; Strabismus; Cornea, External Disease, and Refractive Surgery; Surgical Retina &amp; Vitreous; and Glaucoma.</td>
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<td>The AUPO FCC will help to coordinate the establishment of fellowship requirements and monitor compliance of individual fellowship programs with these requirements. The AUPO FCC will help to coordinate the establishment of fellowship programs in neuro-ophthalmology in the United States, and the full list of compliant programs can be accessed at <a href="http://www.aupofcc.org">http://www.aupofcc.org</a>. The NANOS Professional Standards Committee (a Fellowship Education Committee is a requirement to participate in the AUPO FCC) meets at the annual NANOS meeting. At that meeting, the AUPO FCC standards and requirements for neuro-ophthalmology fellowship training are discussed, and revisions are made and approved as needed. The committee discusses the ongoing issues of participation or nonparticipation in the SF Match and other questions related to the AUPO FCC process and professional standards. Now that there are 19 AUPO FCC compliant fellowship programs in neuro-ophthalmology in the United States, 2 major issues will have to be dealt with by the NANOS Board of Directors: 1) Is it fair and appropriate for fellowship applicants to continue not to have NANOS participate in some type of formal matching process? 2) In the future, should full fellows in NANOS be required to be trained only by programs that are AUPO FCC compliant? These are difficult questions that merit continued discussion and debate. We have had very positive feedback on the AUPO FCC process from participating fellows (through fellow exit surveys) and participating programs. We believe that the standardization and oversight offered by the AUPO FCC has improved graduate medical education in neuro-ophthalmology and has provided the intended protection for the trainees, the programs, and most importantly the patients. We are delighted that this editorial is being published in March 2015, exactly 10 years since formal implementation of the AUPO FCC process!</td>
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AUPO, Association of University Professors in Ophthalmology; FCC, Fellowship Compliance Committee.
Transparency, Reproducibility, and Validation: Raising the Quality of Reporting in the Journal of Neuro-Ophthalmology

Jason L. Roberts, PhD, Larissa Shamseer, MSc

For readers to assess the validity of research and replicate its results or for editors to effectively judge the accuracy and true potential impact of an article, authors must carefully—and comprehensively—document their study methodology and findings. Sadly, as has been repeatedly recorded, failure to report essential methodological elements is prevalent across the biomedical literature (1–3), including neurology (4,5) and ophthalmology (6–9). At the level of an individual article, lack of description as to how a study was conducted, which criteria were used to select patients, or, for research syntheses, how the literature search was structured and executed are inconvenient. Amplified across an entire field of study, poor reporting can elevate weak, unsound, or simply specious evidence, with the undesirable potential to misdirect future research up scientific cul-de-sacs.

Complete descriptions of the purpose and results in a research study should never be an afterthought. Indeed, every author should consider the issues of reporting research methods and findings from the moment the article is conceived. Fortunately, an array of tools to assist authors exists in the form of reporting guidelines. The most well known of these are CONSORT 2010 (Consolidated Standards of Reporting Trials) (10,11), STROBE (Strengthening the Reporting of Observational studies in Epidemiology) (12,13), and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (14,15). Reporting guidelines, which are evidence- and consensus-based, and usually designed, tested, and validated by world-renowned methodology experts, pinpoint core components for reporting a particular type of study. They might quite simply be defined as an approach to encourage the provision of carefully structured minimum elements of information within a research report/article. Such reporting guidelines are commonly known in their distilled form: checklists and, in some cases, algorithms. It is these checklists that the Journal of Neuro-Ophthalmology has decided to use in an effort to raise its reporting standards.

Presently, close to 600 biomedical and health research journals have endorsed CONSORT for authors who submit the results of clinical trials for publication (16). Evidence shows that trials published in journals following these guidelines are more completely reported (17). Similarly, data are emerging demonstrating a positive effect of PRISMA endorsement on systematic review articles (18).

Starting in the spring of 2015, the Journal of Neuro-Ophthalmology will strongly encourage authors to include reporting criteria within their articles. The journal will request that authors adhere to the appropriate reporting guideline checklist and indicate where specific reporting elements can be found in their submissions. Checking for adherence to these reporting standards will become a feature of the Journal of Neuro-Ophthalmology peer review and editorial decision-making process.

The Journal of Neuro-Ophthalmology is not striking out alone on this matter. Nine of the top 10 general medical journals (by impact factor) endorse the use of relevant reporting guidelines. In 2014, Neurology declared that all submissions would be required to use a reporting guideline checklist and demonstrate adherence as part of its peer review process (19). The American Journal of Ophthalmology, in its Instructions for Authors, insists that all randomized controlled trials must show adherence to the CONSORT statement and provide an algorithm of the flow of participants throughout the trial (20).

Editorial Office (JR), Journal of Neuro-Ophthalmology, Plymouth, Massachusetts; Department of Neurology (JR), Dartmouth Hitchcock Medical Center, Lebanon, New Hampshire; Ottawa Hospital Research Institute (LS), Ottawa, Ontario, Canada; and University of Ottawa (LS), Ottawa, Ontario, Canada.

The authors report no conflicts of interest.

Address correspondence to the Journal of Neuro-Ophthalmology Editorial Office, 36 Old Mill Lane, Plymouth, MA, 02360. E-mail: jneuroophthalmol@gmail.com

However, as of December 2014, a quick investigation showed that only 4 of the top 10 journals (by impact factor) in the clinical neurosciences and 3 of the top 10 in ophthalmology endorse the use of any reporting guideline.

The movement to raise reporting standards is not solely a journal-led exercise. In October 2014, the National Institutes of Health, along with Nature Publishing Group and Science, promoted a core set of reporting standards in preclinical work to ensure the reproducibility of results, building on an earlier call for action on the issue (21,22). There is a growing consensus that key funding agencies will eventually take the next step and insist on compliance to these validated measures of reporting for the research they fund.

So, what does this mean for authors? First and foremost, reporting guidelines, although sometimes perceived as such, are not barriers to submission. Although it may be frustrating after composing an article to have to go back to include missing information, it must be remembered that an article is only strengthened as a result of such an exercise. Ultimately, we want authors to compose their articles using reporting guidelines as a writing aid, rather than an afterthought. Furthermore, rare is the article that completes peer review without some form of amendment and revision. Indeed, rather than necessarily reviewing for adherence to reporting standards in a gatekeeper capacity (i.e., should a manuscript be accepted or rejected?), the Journal of Neuro-Ophthalmology intends to use the reporting guidelines to work with authors to polish their articles.

Authors should also be cognizant that these guidelines are designed to be portable across journals and even fields of study. Should a submission be rejected by the Journal of Neuro-Ophthalmology, having followed the reporting guidelines will only serve the article well at the next journal to which it is submitted.

With the launch of a new campaign to raise reporting standards, the Journal of Neuro-Ophthalmology will now provide reporting guideline templates both from within its online Instructions for Authors and from within the Editorial Manager submission system. The checklists can also be downloaded from the EQUATOR Network site (www.equator-network.org). The hope is that authors will provide a completed reporting guideline checklist. The reporting guideline template will, in turn, then be provided to the peer reviewers. Where gaps in the depth of reporting are found, the journal will expect authors to address these alongside other requests for revision.

In many professions, checklists are used to ensure accuracy, completeness, and transparency. Biomedical reports, especially when considering what is at stake, should similarly adopt such practices. The Journal of Neuro-Ophthalmology believes that by requesting adherence to higher reporting standards, authors will benefit by creating a better manuscript. Readers of the journal similarly gain by reading articles that have been vetted using the best tools available to ensure high reporting standards. It should be expected that the field of the neuro-ophthalmology will be better served, and it is hoped that all stakeholders embrace a commitment to a higher level of academic scholarship.

REFERENCES


Vision in a Phase 3 Trial of Natalizumab for Multiple Sclerosis: Relation to Disability and Quality of Life

Salim Chahin, MD, Laura J. Balcer, MD, MSCE, Deborah M. Miller, PHD, Annie Zhang, MD, MPH, Steven L. Galetta, MD, FAAN

Background: Low-contrast visual acuity (LCVA), a sensitive measure of visual function in multiple sclerosis (MS), demonstrated treatment effects as a secondary outcome measure in the Phase 3 trial of natalizumab, AFFIRM. In these posttrial analyses, we studied the relation of visual function to quality of life (QOL), magnetic resonance imaging (MRI) measures, and Expanded Disability Status Scale (EDSS) scores.

Methods: At baseline and at 52 and 104 weeks in AFFIRM, patients underwent binocular testing of LCVA (1.25% and 2.5% contrast) and high-contrast visual acuity (HCVA). Vision-specific QOL was assessed by the Impact of Visual Impairment Scale (IVIS), whereas the SF-36 Health Survey and Visual Analog Scale were administered as generic QOL measures and the EDSS as a measure of neurologic impairment.

Results: Among QOL measures, IVIS scores showed the most significant correlations with visual dysfunction at all time points in the trial ($r = -0.25$ to $-0.45$, $P < 0.0001$ for LCVA and HCVA). Higher MRI T1- and T2-lesion volumes were also associated with worse vision scores at all time points ($P < 0.0001$). Clinically meaningful worsening (progression) of LCVA was noted in substantial proportions of patients in AFFIRM and was prevalent even among those without EDSS progression over 2 years (21.9% with LCVA progression at 2.5% contrast; 26.2% at 1.25% contrast). HCVA worsened in only 3.7% of patients without EDSS progression.

Conclusions: Loss of visual function, particularly as measured by LCVA, was common in AFFIRM, occurring in >20% of patients. Both LCVA and HCVA scores reflect vision-specific aspects of QOL, but LCVA provides information about disability progression not entirely captured by the EDSS. Vision represents a key dimension of outcome assessment for MS and adds valuable information on disability and QOL that can be useful to clinicians.

Patients with multiple sclerosis (MS) experience a variety of symptoms that can affect quality of life (QOL) and contribute to disability (1,2). Visual impairment is a common symptom in MS with up to 50% of patients developing optic neuritis and up to 77% of patients manifesting subclinical changes in visual function (3–7). To that extent, visual function, specifically low-contrast visual acuity (LCVA), has emerged as an important candidate in MS that captures aspects of the disease not routinely quantified by disability or QOL measures (3,8,9).

The Expanded Disability Status Scale (EDSS) is the leading disability measure in MS (10,11). The EDSS includes high-contrast visual acuity (HCVA) but does not capture all aspects of visual dysfunction and, at higher disability levels, is geared more towards physical dysfunction (10,11). Similarly, generic QOL measures, such as Short Form-36 (SF-36) capture overall but not vision-specific, decline in QOL (1,2). Furthermore, the influence of visual dysfunction on these QOL measures is not well studied (1,2).
Despite the prevalent use of visual function testing (VFT), EDSS and QOL metrics, neurologists, and neuro-ophthalmologists continue to face the challenge of incorporating these outcome measures when evaluating for disease progression (4,5,12). Exploring associations between LCVA, disability, QOL, and magnetic resonance imaging (MRI) can help bridge this gap in our knowledge and provides further support for a multidimensional approach to MS symptoms. In the Phase III, placebo-controlled AFFIRM trial of natalizumab (Biogen Idec Inc, Weston, MA) (13), LCVA detected treatment effects on sustained visual loss and visual improvement in patients with MS (12,14). Treatment with natalizumab also was associated with improved QOL (1,13), MRI outcomes (13,15–17) and disability (18).

In these post-hoc analyses of AFFIRM data, we provide a novel approach to evaluating LCVA and its association to global disease metrics, including QOL, disability, and MRI outcomes in a large standardized clinical trial setting.

METHODS

We evaluated the association of high and low-contrast vision to the following: 1—Overall QOL, 2—Vision-specific QOL, 3—MRI metrics, and 4—Neurologic impairment.

Patients
The AFFIRM trial included 627 patients randomized to natalizumab and 315 patients randomized to placebo. Key inclusion criteria were male and female patients between 18 and 50 years of age, diagnosis of relapsing–remitting multiple sclerosis (RRMS), and baseline EDSS score of 0.0–5.0. Participants also had to have brain MRI lesions consistent with MS and at least 1 medically documented relapse within 12 months before study start date (13). Exclusion criteria included treatment with cyclophosphamide or mitoxantrone within the previous year or treatment with interferon beta, glatiramer acetate, cyclosporine, azathioprine, methotrexate, or intravenous immune globulin within the previous 6 months. Patients who had received treatment with interferon beta, glatiramer acetate, or both for more than 6 months were also excluded (13). The study protocols were approved by central and local institutional review boards (13).

Visual Function Testing
Binocular LCVA and HCVA were measured using Sloan letter charts at 1.25%, 2.5% (low), and approximately 100% (high) contrast levels (Precision Vision, La Salle, IL). Binocular vision testing scores best reflect daily activities and can be subject to summation or inhibition providing more useful associations with QOL and MRI outcomes that monocular vision (3,9,19). Patients were asked to read each of 3 charts at 2 m using standardized protocols (13,14), and the number of letters identified correctly (maximum of 60 per chart) was recorded (14). Clinically meaningful changes in visual function were defined as a ≥7-letter reduction in score (1,8,12,14). Although both 1.25% and 2.5% low-contrast visual acuity scores were analyzed, 1.25% low-contrast scores are discussed only in cases where results differed between the 2 contrast levels.

Overall and Vision-specific QOL Measures
The following QOL instruments were completed at baseline and at weeks 24, 52, and 104.

SF-36 Health Survey
The SF-36 measures the patient’s general health status from his/her perspective (1,20). It is composed of 8 multi-item scales with scores ranging from 0 to 100. Higher scores indicate better QOL. Resulting data can be used to calculate 2 summary scores: the Physical Component Summary (PCS), consisting of physical functioning, physical role, bodily pain, and general health elements and the Mental Component Summary (MCS), consisting of vitality, social functioning, emotional role, and mental health elements. The PCS and MCS summary scores, used in this analysis, were computed as standardized scores with a mean score of 50 (and SD of 10) corresponding to the US general population.

Visual Analog Scale
The visual analog scale (VAS) measures overall well-being as reported by the patient. To complete the VAS, patients were asked to draw a vertical line on a scale representing “poor” to “excellent” to show “how you feel now.” Responses were converted to a scale of 0–100. Higher scores indicate better self-report QOL ratings (1).

Impact of Visual Impairment Scale
The Impact of Visual Impairment Scale (IVIS), a subscale of the MS Quality of Life Inventory, measures vision-specific QOL. It is a 5-item scale that captures noncognitively based difficulties with visual recognition that cannot be corrected with visual aids. Scores range from 0 to 15, with higher scores representing worse QOL (21) (See Supplemental Digital Content, Table E1, http://links.lww.com/WNO/A111). In AFFIRM, the IVIS was administered to a subset of English-speaking patients only.

MRI Measures
MRI parameters included T1-hypointense, T2-, and gadolinium-enhancing (Gd+) lesion volume; the number of Gd+, new T1, and new T2 lesions; and brain parenchymal fraction (BPF, a measure of brain atrophy).

Neurologic Disability
Neurologic disability was evaluated using the EDSS, an ordered scale that ranges from 0.0 to 10.0 in 0.5-point increments, with higher scores indicating more severe neurologic impairment (10,13). EDSS was scored every 12 weeks during the study period. The EDSS incorporates...
HCVA, relies on the neurologic examination in the early stages of disability and on gait dysfunction in later stages of disability. Untreated patients with MS will progress by 1.0–2.0 points on this scale over 5 years (10,11).

**Statistical Analyses**

In this post-hoc study, unless otherwise noted, the following cross-sectional analyses were performed at baseline and at 52 and 104 weeks for the entire patient cohort, regardless of treatment group.

**VFT and QOL**

Correlations between VFT scores and QOL measures were evaluated using the Pearson correlation coefficient. Linear regression models were used to examine the relation between VFT scores and QOL scores adjusting for baseline age.

**VFT and MRI**

Correlations between VFT score and MRI parameters were evaluated using the Pearson correlation coefficient.

**VFT and Neurologic Disability**

Sustained progression (worsening) was defined as either a $\geq 1.0$-point increase (for patients with baseline scores $\geq 1.0$) or a $\geq 1.5$-point sustained increase (for patients with baseline scores of 0.0) maintained over 12 weeks. Patients with nonsustained changes or changes that did not meet these criteria were categorized as having stable disability.

Agreement between patient groups that had clinically meaningful VFT worsening ($\geq 7$ letters per chart) and EDSS progression was examined using McNemar’s test. Time to 12-week sustained 7-letter visual worsening in VFT scores from baseline among patients with stable EDSS over 2 years was assessed using the Kaplan–Meier method and the Cox proportional hazards model, adjusted for baseline VFT, EDSS, and age.

A composite measure of disease progression that included both EDSS and 7-letter visual progression was analyzed in a Cox proportional hazards model to determine its sensitivity to treatment effect.

**RESULTS**

A total of 942 patients (627 in the natalizumab group and 315 in the placebo group) were enrolled in the AFFIRM trial. Table E2 (see Supplemental Digital Content, http://links.lww.com/WNO/A112) summarizes baseline age, VFT scores, QOL, MRI measures, and disability scores.

**Association Between VFT Scores and QOL**

Cross-sectional correlation analyses at baseline, 52 weeks, and 104 weeks showed a consistent pattern of correlations between reduced visual function and worse QOL scores (See Supplemental Digital Content, Table E3, http://links.lww.com/WNO/A113). Worse PCS and IVIS scores were modestly but consistently associated with lower VFT scores at all time points, with linear correlations ranging from 0.08 to 0.14 for the PCS ($P < 0.05$) and $-0.25$ to $-0.45$ for the IVIS ($P < 0.0001$). In fact, among all QOL measures, IVIS showed the strongest and the most significant correlations with vision, with worse IVIS scores occurring in patients with worse visual function.

At each time point, SF-36 MCS and VAS scores were reduced among patients with worse scores for LCVA but not for HCVA (correlations: 0.08–0.09 for PCS, $P < 0.05$; 0.09–0.13 for VAS, $P < 0.01$) except for the 104-week time point, where VAS scores were significantly correlated with HCVA ($r = 0.08; P < 0.01$).

At baseline, linear regression analyses showed that 7-letter reductions in 2.5% LCVA and HCVA scores were associated with a 0.5-point and 1.3-point worsening of vision-specific QOL by the IVIS, respectively ($P < 0.001$).

**Association Between VFT Scores and MRI Measures**

At baseline and at 52 and 104 weeks, there were modest and significant correlations between worse VFT scores and higher T1- and T2-lesion volumes ($P < 0.0001$) (See Supplemental Digital Content, Table E4, http://links.lww.com/WNO/A114). Better LCVA scores were correlated with lower Gd+ lesion volume and number at baseline but this was not observed for HCVA. In addition, better LCVA scores were associated with a lower number of new T1 and T2 lesions at 1 year ($P < 0.01$) and higher BPF.

**Association Between VFT Scores and Disability**

At 2 years, the proportions of patients with visual worsening as measured by HCVA were significantly different between patients with and without EDSS progression (Fig. 1). The proportions of patients with visual progression as measured by LCVA (2.5% and 1.25%) were not significantly different between patients with and without EDSS progression. Notably, substantial proportions of patients without EDSS progression still had visual progression at 2.5% and 1.25% contrast on LCVA (21.9% and 26.2%, respectively). A composite measure of disease progression including both VFT and EDSS scores showed sensitivity to natalizumab treatment effects. Specifically, 34% relative reduction was seen in cumulative probability of either EDSS or HCVA progression in patients treated with natalizumab relative to placebo (hazard ratio [HR], 0.66; 95% confidence interval [CI], 0.50–0.86; $P = 0.002$) (See Supplemental Digital Content, Table E5, http://links.lww.com/WNO/A115). A 32% relative reduction was seen in the cumulative probability of either EDSS or LCVA (2.5%) progression (HR, 0.68; 95% CI, 0.55–0.84; $P = 0.0003$) in patients treated with natalizumab.
DISCUSSION

These results from the Phase 3 trial of natalizumab (AFFIRM) show that even among this group of patients with relatively early RRMS, visual dysfunction is associated with reductions in QOL. Important measures of overall disease activity, including MRI lesion burden, are higher in those with reduced vision. Neurologic disability, however, as measured by EDSS progression did not seem to capture all patients with clinically meaningful visual loss. This disconnect between EDSS and visual progression occurred only for LCVA, providing evidence that this visual measure captures aspects of neurologic impairment not entirely captured by the EDSS.

A greater understanding of the relation between vision, neurologic disability, and QOL, as illustrated in this study, adds to the body of evidence on LCVA as a measure of visual dysfunction that is associated with QOL (22), MRI (23,24), and retinal neuronal and axonal thinning (25–27) and will help clinicians to incorporate LCVA as a measure of impairment in clinical practice (1,3,5).

QOL measures are objective outcomes that may be influenced by several factors (1,2). Our study further validates the use of these measures in the context of visual impairment and explores the complex relationship between high- and low-contrast vision and the different measures of QOL. Modest associations were observed over time between reduced VFT and QOL measures. Although reductions in LCVA scores were significantly associated with worse scores for all QOL measures at all time points in the AFFIRM trial, HCVA scores were associated with only PCS and IVIS at all time points and with VAS only at 2 years.

Seven-letter changes in LCVA and HCVA scores were associated with substantial changes in IVIS scores, indicating a strong association with this vision-specific QOL parameter. HCVA had stronger correlations with IVIS. Our findings confirm the associations seen by Mowry et al (22) with the advantage of standardized testing in a clinical trial setting and reflect the fact that HCVA deficits are more noticeable to patients and thus greatly affect vision-specific QOL, whereas LCVA changes are more subtle but yet may impact many aspects of patients’ lives. Interestingly, both the IVIS used in the study and the NEI-VFQ-25 used by Mowry et al (22) showed significant associations with visual function. The NEI-VFQ-25 is more commonly used (22,28). However, both scales are well validated and can be used to capture vision-specific QOL.

Although the correlations between LCVA and MRI metrics were the modest, they tended to persist over the course of the trial. Wu et al (24) demonstrated correlations between LCVA and MRI T2-lesion burden and between HCVA and BPF. Reduced LCVA has also established associations with neuronal and axonal loss captured by OCT (25–27). Our findings provide further evidence that visual dysfunction reflects MRI lesion burden and brain atrophy (23,24) and can be used to reflect disease activity.

Of interest, LCVA but not HCVA detected visual loss even in patients without EDSS progression. HCVA may not detect visual loss in patients without EDSS progression because HCVA changes may influence the total disability score, especially at lower EDSS scores (10,11). LCVA, however, is not measured by the functional systems that make up the EDSS and provides information about visual function not captured by the EDSS (23). Furthermore, the EDSS may not be sensitive to subtle changes in certain disease aspects especially in patients with more physical disability of gait impairment (10,11). Thus, LCVA could
be capturing other aspects of disease activity that are not well measured by the EDSS.

Our results add vision-specific data to recent analyses on disability data from the AFFIRM trial that showed that sustained improvements in EDSS scores were associated with improvements in patient-reported QOL measures for both the PCS and MCS (18) and expand our knowledge on how vision, specifically LCVA, along with vision-specific QOL measures, provide added value to our understanding of QOL and disability.

The AFFIRM trial did not capture other comorbid ocular conditions; however, in this relatively young patient population, conditions that affect LCVA are uncommon and unlikely to affect our results (3,8). The trial did not capture history of acute ON before or during the study period. To be eligible, patients were required to be relapse-free within 50 days of the first dose and to have a stable EDSS score. Capturing acute events of ON will be important for interpreting mechanisms for visual loss and improvement in ongoing and future trials, which now routinely include structural and functional measures of vision.

REFERENCES


Association Between Phosphodiesterase-5 Inhibitors and Nonarteritic Anterior Ischemic Optic Neuropathy

Nawaaz A. Nathoo, MD, Mahyar Etminan, PharmD, MSc, Frederick S. Mikelberg, MD, FRCSC

Background: Use of phosphodiesterase-5 (PDE-5) inhibitors has been reported to be a risk factor for development of nonarteritic anterior ischemic optic neuropathy (NAION) in males, based largely on a number of case reports. The objective of our study was to determine whether men who use this class of medications are more likely than a matched control group to develop NAION.

Methods: A pharmacoepidemiological nested case–control study was used to examine the above association in a health claims database of physician diagnoses and prescription medication dispensing. Cases of NAION were matched with corresponding controls and correlated with the use of PDE-5 inhibitors. A conditional logistic regression model was used to estimate rate ratios for development of NAION with use of PDE-5 inhibitors.

Results: A total of 1,109 cases of NAION were found and matched to 1,237,290 controls identified within the database. Cases were more likely to have hyperlipidemia, diabetes, hypertension, myocardial infarction, and cerebrovascular accident in the year preceding their NAION. The adjusted rate ratio for any use of PDE-5 inhibitor in the year before the NAION was 1.01 (95% confidence interval [CI], 0.79–1.28); recent use of a PDE-5 inhibitor in the 30 days before the NAION also had no significant association, with an adjusted rate ratio of 0.96 (95% CI, 0.75–1.23). Results for individual PDE-5 inhibitors did not achieve statistical significance.

Conclusions: Our results do not suggest any association between having a prescription filled for PDE-5 inhibitor medication and receiving a diagnosis code for NAION. This is consistent with other studies in the literature that have failed to elucidate a plausible mechanism by which these drugs might compromise circulation at the optic nerve head.

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Nonarteritic anterior ischemic optic neuropathy (NAION) is an optic neuropathy believed to be caused by ischemia to the optic nerve head. Its pathophysiology is thought to be related to compromised circulation through the short posterior ciliary arteries due to episodes of hypotension (including nocturnal hypotension) and underlying vascular disease (hypertension, diabetes mellitus dyslipidemia). Eyes with small crowded optic discs with small or nonexistent cupping also seem to be at greater risk, likely due to mechanical obstruction leading to decreased blood flow (1).

Several medications also have been implicated in causing NAION, although evidence of true causation is often lacking (1). Many case reports have suggested a link between phosphodiesterase-5 (PDE-5) inhibitors (sildenafil, tadalafil, and vardenafil) and NAION, largely through an observed temporal relationship between use of these medications and subsequent development of NAION (2–8). These medications act by inhibiting the degradation of phosphodiesterase in the smooth muscle cells lining the corpus cavernosum of the penis, leading to accumulation of cyclic guanosine monophosphate, causing release of nitric oxide and subsequent vasodilation (9). The PDE enzyme is found in smooth muscle of many vascular tissues in the body, but the PDE-5 subtype, on which these drugs preferentially act, is found only in the corpus cavernosum. A different subtype, PDE-6, is found in retinal blood vessels and sildenafil and vardenafil have been shown to have selectivity for these receptors as well; this is likely the mechanism for the transient changes in color perception that are commonly recognized side effects of these medications (9).
These medications are also being explored as therapies for pulmonary arterial hypertension, as they have been shown to have some vasodilatory effects on pulmonary vasculature (10). However, there is little evidence that they impact circulation at the optic nerve head or in the short posterior ciliary arteries (11,12).

Epidemiological studies have examined the association of PDE-5 inhibitors with NAION and found no association (13), and there are Phase-III clinical trials examining the ocular safety of sildenafil (14). Limitations exist in these reports such as short follow-up periods and lack of adjustment for confounding variables. Therefore, further study is warranted.

The purpose of this study was to use a health claims database to determine whether patients who have developed NAION had a greater likelihood than the general population of using PDE-5 inhibitors before development NAION.

**METHODS**

We used the IMS Lifelink database as the data source for this study. Lifelink is a health claims database that captures prescription drug dispensing, physician visits, hospitalizations, and demographic information for approximately 68 million residents of the United States. The database captures 17% of males aged 45–54 years, 13% of males aged 55–64 years, and 8% of males aged >65 years. Information on all physician visits and hospitalizations are entered as International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. The data for this study were comprised of approximately 1 million men randomly selected from the database followed from 2000 to 2011. The database has been subject to routine quality checks and has been used in previous pharmacoepidemiologic research (15,16). Institutional review board approval was obtained for this study.

**Case and Control Definition**

Cases were defined as those with the first ICD-9 diagnosis of NAION (ICD-9 code 377.41). The date of the first diagnosis of NAION (registration of code 377.41) was deemed the index date. We excluded patients with history or subsequent diagnosis of polymyalgia rheumatica and giant cell arteritis. For each case, all eligible controls with no history of NAION were identified and matched to the cases by age, calendar time, and index date of the case. Since a density-based sampling strategy was used for control selection, each control could have been used more than once. This type of sampling ensures that the odds ratio is a close approximation of the rate ratio (17). Demographic information was examined using descriptive statistics, and a conditional logistic regression model was built to examine rate ratios.

**RESULTS**

Within the initial cohort of 934,283 individuals, a total of 1,109 cases of NAION diagnosis were found and matched to 1,237,290 age-matched controls. The average age of both groups was 69.8 years; cases were more likely to have been taking medication for hyperlipidemia and were more likely to have been diagnosed with diabetes mellitus, hypertension, myocardial infarction, and stroke. Adjusted rate ratios were computed with non-users of PDE-5 inhibitors (in the year before the index date) as the control group.

**Statistical Analysis**

Demographic information was examined using descriptive statistics. Recent users of a PDE-5 inhibitor drug were defined by having 1 prescription of sildenafil, vardenafil, or tadalafil filled within 30 days of the index date. “Any use” was defined as a subject who had filled a prescription for a study anytime in the 1 year before the index date. We further stratified our analysis to the type of a PDE-5 inhibitor where a user was defined as a subject who had received at least 1 prescription of either sildenafil, vardenafil, or tadalafil within 1 year of the index date. A conditional logistic regression model was created to adjust for the following covariates: diabetes, statins, hypertension, myocardial infarction, and stroke. Adjusted rate ratios were calculated for potential confounders.

**DISCUSSION**

The results of this large retrospective case–control study support the lack of association between NAION and PDE-5 inhibitor use. Similarly, Margo and French (13) conducted a large case–control study in a large cohort of 4 million veteran patients of 50 years or older in the United States from 2004 to 2005 and did not find an increase in the risk of NAION (rate ratio = 1.02; 95% CI, 0.92–1.12) with sildenafil users. The limitations of this study were its relatively short follow-up and lack of adjustment for potential confounding variables, which were addressed by our study with a longer follow-up period (12 years) and adjustment for potential confounders.
A collated review of over 14,000 cases of sildenafil demonstrated no increased incidence of NAION over the general population (18), which is in agreement with our findings. Similarly, Wirostko et al (14) examined the ocular safety of chronic sildenafil use in a 12-week, double-blind, randomized, placebo-controlled, Phase-III trial where 277 men with idiopathic pulmonary arterial hypertension were prescribed oral sildenafil (20, 40, or 80 mg) or placebo and followed for 18 months. Ocular adverse events were examined using ophthalmic examinations, visual function tests, patients’ reports of adverse events, and adverse events reported by investigators. At the end of 18 months, none of the groups taking sildenafil were found to have NAION.

In contrast, a retrospective study of men with NAION was conducted in which men with NAION were asked about their PDE-5 inhibitor history; 671 men were found to have NAION without a history of PDE-5 inhibitor use, whereas 43 did have definite NAION and PDE-5 inhibitor use in the 1-day preceding it. This study found an odds ratio of 2.15 for PDE-5 inhibitor use in NAION (95% CI, 1.06–4.34; P = 0.033) (19).

Although our data show a trend toward varying relationships of each PDE-5 inhibitor medication with NAION (adjusted rate ratio for tadalaafil of 0.74, for vardenafil of 1.47), none of these associations reached statistical significance.

There are 2 principle mechanisms proposed by which PDE-5 inhibitors may cause NAION: first, they cause systemic hypotension and second, they cause impaired local autoregulation at the optic nerve head in the short posterior ciliary arteries (20). However, neither of these have been conclusively proven or even supported by animal models and human trials (11,12,20).

The only studies present in the literature that have suggested a causal relationship are case reports, with no other clinical studies that have confirmed this apart from the retrospective study noted above. To the contrary, clinical studies have examined the effect of PDE-5 inhibitor use on ocular blood flow, including flow at the short posterior ciliary arteries to the optic nerve head, and these have found either no change in blood flow or the opposite of increased flow (11,12).

The most convincing causal relationship established in the literature is a rechallenge in 1 patient who reported...
transient monocular visual field defects on 4 occasions followed by a persistent monocular visual field defect, each occurring within hours of taking tadalaflit; the patient was diagnosed with NAION when he sought medical attention for the persistent defect (3). In a series of 10 patients who developed sequential NAION while on PDE-5 inhibitors, Galvez-Ruiz and Arishi (21) were not able to confirm or exclude whether it was the PDE-5 inhibitor, or other risk factors, that most likely contributed to sequential NAION. No other evidence in the literature supports the association so strongly, and most patients reported in the other case reports had 1 or more established risk factors for NAION (2–6,8).

As with all observational studies, our report is subject to limitations. As with all studies using administrative data, we could only assess PDE-5 inhibitor use through prescription drug dispensation in the database, which does not necessarily correlate with use and certainly does not indicate the timing of use, given that PDE-5 inhibitors are not chronic daily-use medications. Nevertheless, with such a large number of patients included, it can be inferred that filling a prescription in the 1 month or 1 year before the event should correlate with use of the medication in most patients. In addition, although our study was adequately powered to show no association with PDE-5 inhibitors and NAION, it was underpowered for the association with specific PDE-5 inhibitor medications. Finally, due to the nature of the data collected through the database, medications purchased out of insurance plans were not captured in the analysis, either for the case or control groups.

In summary, we found no association between having a prescription filled for a PDE-5 inhibitor medication and receiving a diagnosis code of NAION. Although PDE-5 inhibitors are known to affect retinal circulation and thereby cause transient changes in color perception, there is no epidemiological association with NAION, nor is there any support in the literature for the proposed mechanisms of their adverse effect on the circulation of the optic nerve head.

STATEMENT OF AUTHORSHIP

REFERENCES
Clinical Evaluation of Eye Movements in Spinocerebellar Ataxias: A Prospective Multicenter Study

M. Moscovich, MD, Michael S. Okun, MD, Chris Favilla, BS, Karla P. Figueroa, MS, Stefan M. Pulst, MD, Susan Perlman, MD, George Wilmot, MD, PhD, Christopher Gomez, MD, PhD, Jeremy Schmahmann, MD, Henry Paulson, MD, PhD, Vikram Shakkottai, MD, PhD, Sarah Ying, MD, PhD, Theresa Zesiewicz, MD, S. H. Kuo, MD, PhD, P. Mazzoni, MD, PhD, Khalaf Bushara, MD, Guangbin Xia, MD, PhD, Tetsuo Ashizawa, MD, S. H. Subramony, MD

Background: Ocular motor abnormalities reflect the varied neuropathology of spinocerebellar ataxias (SCAs) and may serve to clinically distinguish the different SCAs. We analyzed the various eye movement abnormalities detected prospectively at the baseline visit during a large multicenter natural history study of SCAs 1, 2, 3, and 6.

Methods: The data were prospectively collected from 12 centers in the United States in patients with SCAs 1, 2, 3, and 6, as part of the Clinical Research Consortium for Spinocerebellar Ataxias (NIH-CRC-SCA). Patient characteristics, ataxia rating scales, the Unified Huntington Disease Rating Scale functional examination, and clinical staging were used. Eye movement abnormalities including nystagmus, disorders of saccades and pursuit, and ophthalmoparesis were recorded, and factors influencing their occurrence were examined.

Results: A total of 301 patients participated in this study, including 52 patients with SCA 1, 64 with SCA 2, 117 with SCA 3, and 68 with SCA 6. Although no specific ocular motor abnormality was pathognomonic to any SCA, significant differences were noted in their occurrence among different disorders. SCA 6 was characterized by frequent occurrence of nystagmus and abnormal pursuit and rarity of slow saccades and ophthalmoparesis and SCA 2 by the frequent occurrence of slow saccades and infrequent nystagmus and dysmetric saccades. SCA 1 and SCA 3 subjects had a more even distribution of eye movement abnormalities.

Conclusions: Prospective data from a large cohort of patients with SCAs 1, 2, 3, and 6 provide statistical validation that the SCAs exhibit distinct eye movement abnormalities that are useful in identifying the genotypes. Many of the abnormalities correlate with greater disease severity measures.

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Spinocerebellar ataxias (SCAs), by convention, denote a group of progressive autosomal dominant disorders that are genetically, clinically, and pathologically heterogeneous. Both cerebellar and extracerebellar involvement may occur accounting for the complex clinical picture of the SCAs (1–3). SCAs are associated with a variety of abnormalities in eye movements; some of these results from abnormalities in cerebellar control, whereas others reflect extracerebellar pathology. Previous publications have documented the type of abnormalities noted in families examined during gene identification studies, in small scale reports using eye movement recordings (4–10) and in larger patient cohorts of SCA subjects (11,12). We summarize the findings of bedside ocular motor examination performed prospectively in a large cohort of patients with SCAs 1, 2, 3, and 6 and examine factors that may influence their presence. Such data may provide clues...
for obtaining the appropriate diagnostic gene testing and provide information as to the neuronal subsets involved in each disorder.

METHODS

Clinical Method

Data were collected prospectively during an NIH-funded natural history study on SCAs 1, 2, 3, and 6, conducted at 12 U.S. centers as part of the Clinical Research Consortium for Spinocerebellar Ataxias (CRC-SCA) (13). This is one of the 19 rare disease consortia of the Rare Disease Clinical Research Network. The protocol was approved by local ethics committee at each institution, and informed consent was obtained from all participants.

Inclusion criteria were 1) DNA diagnosis of SCAs 1, 2, 3, or 6 in the study subject or his/her affected family member(s); 2) phenotype consistent with the DNA diagnosis; 3) willingness to participate in the study; and 4) age of ≥6 years. The exclusion criteria were 1) known recessive, X-linked or mitochondrial ataxia; 2) concomitant disorder(s) that affect Scale for Assessment and Rating of Ataxia (SARA) and other ataxia measures used in this study (e.g., additional neurological illness such as stroke or significant orthopedic disease); and 3) exclusion of SCAs 1, 2, 3, and 6 by DNA testing. At the baseline visit, a complete neurological examination was performed using preformatted case-report forms (CRFs) in which several distinct features of all neurological deficits were recorded by neurologists experienced in the field of ataxia. Eye movement examination used accepted bedside techniques (14) and included pursuit in all directions, examination of horizontal and vertical saccades for both speed and accuracy, careful examination of completeness of eye movements in all directions with urging of the patients to move eyes fully, and detection of nystagmus in primary position and eccentric gaze. The CRFs were used to record all these specific features of eye movements. Ataxia was quantified using SARA (15) and functional status using the Unified Huntington Disease Rating Scale (UHDRS, with permission from the Huntington Study Group). The mobility status was rated using a functional stage classification (16). Blood samples were collected from participants for a reanalysis and confirmation of their mutation status (Laboratory of Stefan M. Puls, Salt Lake City, UT) and additional gene-modifier studies. The subjects were recruited during the period spanning from July 2009 to May 2012.

Genetic Testing

In 263 patients, the size of the respective cytosine–adenine–guanine (CAG) expansion responsible for the SCA was estimated in one of the investigator’s laboratory (S.M.P.). DNA was extracted using a Qiagen FlexiGene DNA Kit (Qiagen, Valencia, CA). CAG repeat lengths were determined by multiplex polymerase chain reaction followed by capillary electrophoresis with internal standards. DNAs were tested for the presence of mutant alleles in the SCAs 1, 2, 3, and 6 genes. Regenotyping and Sanger sequencing were performed for verification of repeat length on 10% of all samples. Two CEPH DNA samples (1331-02 and 1347-02) were included in every run for every marker as an additional internal sizing control. In an additional 38 patients whose samples were not available in the research laboratory, the values from commercial laboratory results were used.

Statistical Analysis

In the analysis of demographic features, specific SCA subtypes (1, 2, 3, and 6) were compared using $\chi^2$ tests for categorical variables, analysis of variance for continuous variables, and Kruskal–Wallis for ordinal variables. The prevalence of various eye movements among the SCA subtypes was then compared with $\chi^2$ tests. To assess the significance of the number of repeats on disease onset and clinical outcome scores, regression analyses were performed. Specifically, linear regression was performed for continuous variables, but ordered logistic regression was used in the assessment of ordinal variables. Logistic regression was used to assess the relationship between number of repeat and the prevalence of various eye movements. Finally, patients with and without SCA-associated eye movement were compared using $\chi^2$ tests for categorical variables, $t$ tests for continuous variables, and Wilcoxon–Mann–Whitney tests for nonparametric variables. $P$-values were adjusted for multiple comparisons. All statistical analyses were performed with Stata/SE 10.0 (StataCorp, College Station, TX).

RESULTS

A total of 301 subjects were evaluated in this study, including 52 SCA 1, 64 SCA 2, 117 SCA 3, and 68 SCA 6 patients. Demographic features of the group are shown in Table 1. Although there was a wide range of clinical severity, the mean SARA scores and functional stage in these patients reflect a moderately advanced stage of disease. In comparing patients with SCAs 1, 2, 3, and 6, no differences were identified in gender distribution, UHDRS functional examination score, and functional disease stage. However, differences were noted in all other demographic features and SARA scores.

Table 2 summarizes the ocular motor abnormalities seen in our patient cohort. There was no abnormality that was unique to any SCA, but in comparing patients with SCAs 1, 2, 3, and 6, significant differences were identified in the prevalence of each eye movement abnormality. Diplopia as a symptom was most prevalent in SCA 3 and SCA 6 and occurred in fewer than 25% of SCA 1 and SCA 2 patients. Abnormal pursuit was more common in SCA 6 and SCA 3 as was gaze-evoked nystagmus (GEN); nystagmus occurred only in 13% of SCA 2 patients. Inaccurate saccades were noted among all SCA

...
patients, hypermetric saccades being more common than hypometric saccades except in SCA 2. Saccade velocity slowing was noted in 80% of SCA 2 patients and was least common in SCA 6 (11%).

We examined the influence of the following variables on the ocular motor abnormalities: gender, age at examination, age at onset, duration of disease, number of CAG repeats in the expanded alleles, SARA score, and mobility status as assessed using the functional staging. The results are summarized in Table 3.

**DISCUSSION**

Eye movements serve to either acquire novel visual targets on the fovea or to stabilize targets of interest on the fovea; the saccadic, pursuit, and vestibular systems, among others, are important in achieving these goals (17). Many neuronal subsets in both the cerebellum and brainstem play key roles in controlling eye movements, and it is not surprising that patients with SCA have a variety of eye movement abnormalities (18,19). This report summarizes the findings of ocular motor examination “at the bedside” performed in a prospective fashion in a large cohort of subjects with SCAs 1, 2, 3, and 6.

Horizontal GEN was a common finding in SCAs 6, 3, and 1 (in that order) and least common in SCA 2, occurring only in 13% of patients. GEN is almost universal in SCA 6 (7,20–22). The infrequency of GEN in SCA 2 has been noted in other clinical studies (11,12). Eye movement recordings have either not detected GEN in SCA 2 (10) or found it in fewer than 50% of subjects (7,20). The floculonodular lobe is important for gaze holding, and damage to this area would explain GEN. These structures are believed to provide a positive feedback to the ocular motor “integrator” in the brainstem, important for converting the velocity signal of an eye movement to a position command. Pathology in brainstem neurons that serve as integrator of eye movements can also explain the nystagmus (23). Interestingly,

**TABLE 1.** Demographic features of patients with SCA

<table>
<thead>
<tr>
<th></th>
<th>SCA 1 (n = 52); P</th>
<th>SCA 2 (n = 64); P</th>
<th>SCA 3 (n = 117); P</th>
<th>SCA 6 (n = 68); P</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male), n (%)</td>
<td>22 (42%); 0.47</td>
<td>29 (45%); 0.78</td>
<td>58 (50%); 0.45</td>
<td>32 (47%); 0.97</td>
<td>0.84</td>
</tr>
<tr>
<td>Race (white), n (%)</td>
<td>49 (94%); &lt;0.001</td>
<td>50 (78%); 0.41</td>
<td>62 (53%); &lt;0.001</td>
<td>62 (91%); &lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, yr</td>
<td>49.6 (12.5); 0.022</td>
<td>49.3 (13.0); 0.004</td>
<td>51.0 (11.5); 0.011</td>
<td>64.5 (10.8); &lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age of onset, yr</td>
<td>40.5 (11.3); 0.31</td>
<td>35.4 (11.4); &lt;0.001</td>
<td>40.3 (11.4); 0.053</td>
<td>52.6 (9.9); &lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Disease duration, yr</td>
<td>9.2 (7.1); 0.041</td>
<td>13.7 (8.5); 0.003</td>
<td>10.5 (7.2); 0.16</td>
<td>12.1 (9.9); 0.38</td>
<td>0.013</td>
</tr>
<tr>
<td>SARA score</td>
<td>14.0 (6.6); 0.16</td>
<td>17.7 (7.2); 0.004</td>
<td>15.1 (8.9); 0.39</td>
<td>14.8 (7.4); 0.59</td>
<td>0.033</td>
</tr>
<tr>
<td>UHDRS</td>
<td>17.8 (6.2); 0.28</td>
<td>17.1 (6.3); 0.77</td>
<td>16.4 (6.5); 0.23</td>
<td>17.2 (5.7); 0.90</td>
<td>0.60</td>
</tr>
<tr>
<td>Functional stage</td>
<td>2.8 (1.3); 0.11</td>
<td>3.0 (1.2); 0.96</td>
<td>3.1 (1.3); 0.61</td>
<td>3.1 (1.3); 0.37</td>
<td>0.44</td>
</tr>
</tbody>
</table>

Values are reported as mean (SD); P value, unless otherwise noted. The P value under each data point represents a comparison of that particular SCA against all other SCAs. These P-values were calculated with χ² tests for categorical variables, t test for continuous variables, and Wilcoxon–Mann–Whitney test for nonparametric variables. The P value in the final column represents the comparison of each individual SCA (4-group comparison). The final column P value was calculated with χ² tests for categorical variables, analysis of variance for continuous variables, and Kruskal–Wallis for nonparametric variables.

SARA, Scale for Assessment and Rating of Ataxia; SCA, spinocerebellar ataxia; UHDRS, Unified Huntington Disease Rating Scale.

**TABLE 2.** Prevalence of eye movement abnormalities in patients with SCA

<table>
<thead>
<tr>
<th></th>
<th>SCA 1 (n = 56) (P)</th>
<th>SCA 2 (n = 69) (P)</th>
<th>SCA 3 (n = 119) (P)</th>
<th>SCA 6 (n = 72) (P)</th>
<th>P Value Comparing All SCAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diplopia</td>
<td>24 (0.010)</td>
<td>18 (&lt;0.001)</td>
<td>61 (&lt;0.001)</td>
<td>43 (0.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GEN</td>
<td>44 (0.067)</td>
<td>13 (&lt;0.001)</td>
<td>77 (&lt;0.001)</td>
<td>78 (&lt;0.001)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypermetric saccades</td>
<td>41 (0.67)</td>
<td>14 (&lt;0.001)</td>
<td>50 (0.042)</td>
<td>51 (0.056)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypometric saccades</td>
<td>20 (0.13)</td>
<td>28 (0.81)</td>
<td>34 (0.038)</td>
<td>21 (0.19)</td>
<td>0.17</td>
</tr>
<tr>
<td>Slow saccades</td>
<td>47 (0.49)</td>
<td>80 (&lt;0.001)</td>
<td>40 (0.31)</td>
<td>11 (&lt;0.001)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Horizontal</td>
<td>22 (0.63)</td>
<td>15 (0.22)</td>
<td>35 (&lt;0.001)</td>
<td>2 (&lt;0.001)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ophthamoparesis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vertical</td>
<td>28 (0.67)</td>
<td>25 (0.46)</td>
<td>47 (&lt;0.001)</td>
<td>6 (&lt;0.001)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abnormal</td>
<td>45 (0.019)</td>
<td>37 (&lt;0.001)</td>
<td>70 (0.023)</td>
<td>79 (0.001)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Square-wave jerk</td>
<td>11 (0.14)</td>
<td>5 (0.019)</td>
<td>23 (0.004)</td>
<td>17 (0.87)</td>
<td>0.012</td>
</tr>
</tbody>
</table>

Values are reported as % (P). The P value is a comparison of that particular SCA against all other SCAs, as calculated with a χ² test. The final column represents the P value in comparing each individual SCA, as calculated with a 4-group χ² test.

GEN, gaze-evoked nystagmus; SCA, spinocerebellar ataxia.
Ying et al (24) found that the flocculonodular lobe was indeed atrophied in SCA 2 and suggested that gaze-holding functions may not be detected accurately at the bedside in this disease.

Inaccurate saccades were most frequent in SCA 6 and SCA 3 and least so in SCA 2; hypermetric saccades were usually much more common than hypometric saccades. Oculographic studies on more limited numbers of subjects have noted similar findings (7,8). The superior colliculus, brainstem, and cerebellum are involved in a circuitry necessary for online correction of saccade amplitude and its rapid adaptation in different behavioral conditions (17). The function of a saccade is to be simultaneously fast and accurate, especially when the stimulus is unexpected and potentially threatening. The dorsal oculomotor vermis (OMV) (lobules V–VII) and the related fastigial nuclear cells are important for saccadic amplitude and direction; bilateral OMV lesions cause hypometric saccades, and in contrast, bilateral lesions of the fastigial nucleus result in hypermetric saccades (18). Purkinje cells in the OMV discharge before saccades and the fastigial nuclear cells fire before contraversive saccades and late during ipsiversive saccades, providing a “braking” discharge. It is interesting to note that hypermetric saccades were usually more frequent than hypometric saccades except in SCA 2, an observation that confirms the findings of Maschke et al (11). Also in SCA 2, hypometric saccades correlated with poorer functional stage of disease.

In addition to dysmetric saccades, slow saccades were documented in all SCAs, most frequently in SCA 2 and least in SCA 6. This has been reported previously, although in SCA 3 patients, eye movement recordings have suggested that saccade slowing is uncommon (7,10). The paramedian pontine reticular formation is critical for the generation of horizontal saccades, particularly the excitatory burst neurons. A specific loss of the excitatory burst neurons has been documented in a case of SCA 2 (25). In our study, the occurrence of slow saccades was correlated with many measures reflecting higher disease severity (Table 3). This suggests that the saccade generators become involved at a later stage of disease.

Ophthalmoparesis generally was less common than other ocular motor abnormalities; it was least common in SCA 6 and most common in SCA 3. Vertical ophthalmoparesis was more common than horizontal ophthalmoparesis. Other reports have noted much higher prevalence of ophthalmoplegia in SCAs 1, 2, and 3 (11,20). Even in SCA 6, these previous studies documented ophthalmoplegia ranging from 24% to 48% of cases; this was not our experience, and we believe that ophthalmoparesis of a significant nature would be incompatible with SCA 6, although some degree of ocular motor neuron loss has been found in neuropathological studies (26). Whether the decline in ocular motility has an infranuclear or supranuclear origin could not be determined in our study. Higher SARA scores and poorer functional stage correlated with ophthalmoparesis in SCA 1 and SCA 3, indicating the involvement of ocular motor neurons in later stages of disease. Diplopia was a more common symptom not only in SCA 3 but also in SCA 6, but fewer than 25% of SCA 1 and SCA 2 patients had this symptom. Among patients who complained of diplopia, horizontal or vertical ophthalmoparesis was noted least frequently in SCA 6 (4% and 14%, respectively); the respective percentages for horizontal and vertical ophthalmoparesis among patients with

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**TABLE 3. Factors related to various ocular motor abnormalities in patients with SCA types 1, 2, 3, and 6**

<table>
<thead>
<tr>
<th>Ocular Motor Symptom/Abnormality</th>
<th>Disease</th>
<th>Factors Reaching Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diplopia</td>
<td>SCA 3</td>
<td>Longer disease duration, higher SARA score, and poorer functional stage</td>
</tr>
<tr>
<td>Abnormal pursuit</td>
<td>SCA 1</td>
<td>Lower SARA score</td>
</tr>
<tr>
<td></td>
<td>SCA 2</td>
<td>Lower SARA score</td>
</tr>
<tr>
<td>Hypermetric saccades</td>
<td>SCA 1</td>
<td>Higher age and higher age at onset</td>
</tr>
<tr>
<td></td>
<td>SCA 2</td>
<td>Lower SARA score and better functional stage</td>
</tr>
<tr>
<td>Hypometric saccades</td>
<td>SCA 2</td>
<td>Poorer functional stage</td>
</tr>
<tr>
<td>Horizontal ophthalmoparesis</td>
<td>SCA 3</td>
<td>Higher SARA score</td>
</tr>
<tr>
<td>Vertical ophthalmoparesis</td>
<td>SCA 1</td>
<td>Higher repeats, higher SARA score, and poorer functional stage</td>
</tr>
<tr>
<td></td>
<td>SCA 3</td>
<td>Higher repeats, higher SARA score, and poorer functional stage</td>
</tr>
<tr>
<td>Slow saccades</td>
<td>SCA 1</td>
<td>Higher repeats, disease duration, higher SARA score, and poorer functional stage</td>
</tr>
<tr>
<td></td>
<td>SCA 2</td>
<td>Higher SARA score and poorer functional stage</td>
</tr>
<tr>
<td></td>
<td>SCA 3</td>
<td>Higher repeats, disease duration, higher SARA score, and poorer functional stage</td>
</tr>
</tbody>
</table>

SARA, Scale for Assessment and Rating of Ataxia; SCA, spinocerebellar ataxia.

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diplopia in the other SCAs were 31% and 39% in SCA 1, 30% and 50% in SCA 2, and 49% and 63% in SCA 3. Therefore, in addition to ophthalmoparesis, diplopia may be related to other factors such as the role of cerebellum in maintaining conjugate gaze.

Pursuit abnormalities were seen in over 70% of patients with SCA 3 and SCA 6 and in a smaller percentage of SCA 1 and SCA 2 patients. Lesions of the flocculonodular lobe are known to decrease the gain of pursuit movements. A diminished gain of pursuit has been documented by eye movement recordings in all of these SCAs (7,20–22). In SCAs 1 and 2, lower SARA scores correlated with occurrence of pursuit abnormalities. This together with the observations on saccadic velocity abnormalities noted in these diseases suggests that abnormal pursuit becomes more difficult to detect because the saccadic system becomes involved with more severe disease.

Square-wave jerks are involuntary saccades that take the eyes off the target and are followed after a normal intersaccadic interval by a corrective saccade back to the target. The topographic diagnostic value of square-wave jerks is unclear. We found that square-wave jerks (≥10 per minute) to be more prevalent in SCA 3 (23%), but also it was present in SCA 6 (17%), SCA 1 (11%), and in 5% of SCA 2 patients.

In a large clinical study of 526 subjects with SCAs 1, 2, 3, or 6, Jacobi et al (12) found a similar prevalence of abnormal pursuit and GEN as in our report; dyssmetric saccades were found in a larger proportion of subjects with all SCAs in that study but were not reported as being hypermetric or hypometric. In 79 subjects with SCAs 1, 2, 3, and 6, Maschke et al (11) found similar abnormalities (11). However, the following differences were noted from our current observations: all types of ophthalmoparesis were more frequent in all SCAs; pursuit abnormalities were much more frequent in SCA 1 and SCA 2; and GEN was more frequent in SCA 1 and SCA 6.

In conclusion, clinical observations of eye movement abnormalities are useful indicators of different types of SCAs. We provide data regarding factors that influence the occurrence of these abnormalities and point to early or late involvement of neuronal populations in different SCAs. This is supported by the limited data available on the neuropathology of these SCAs (25,26). More detailed, longitudinal, and quantitative observations may further clarify these observations.

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REFERENCES


Perimetry, Retinal Nerve Fiber Layer Thickness and Papilledema Grade After Cerebrospinal Fluid Shunting in Patients With Idiopathic Intracranial Hypertension

Jennifer L. Rizzo, MD, Khoa V. Lam, BS, Michael Wall, MD, Machelle D. Wilson, PhD, John L. Keltner, MD

Background: To investigate the effect of cerebrospinal fluid (CSF) shunting on quantitative perimetry and papilledema in patients with uncontrolled idiopathic intracranial hypertension (IIH).

Methods: We retrospectively reviewed all cases of IIH with CSF shunting at our institution between 2004 and 2011. Perimetry was performed before and after surgery in 15 patients, and the mean deviation (MD) was compared before and after surgery to assess the effect of the intervention.

Results: Fourteen of the IIH patients were female and 1 was male. The average age was 34 years. CSF shunting resulted in significant improvement in the perimetric results with an increase in the MD of 5.63 ± 1.19 dB (P < 0.0001). Additionally, average retinal nerve fiber layer (RNFL) thickness measurement by optical coherence tomography decreased by 87.27 ± 16.65 μm (P < 0.0001), and Frisen papilledema grade decreased by 2.19 ± 0.71 (P < 0.0001).

Conclusions: Our results suggest that CSF shunting results in improvement in perimetry, RNFL swelling, and papilledema grade in patients with IIH.

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Greater than 90% of patients with idiopathic intracranial hypertension (IIH) experience visual field loss on static or kinetic perimetry, and it may become permanent (1). Because the disease can progress rapidly and result in irreversible visual loss, it is imperative to monitor and treat patients with IIH promptly and effectively. Patterns of perimetric field loss often resemble glaucoma, including generalized depression of the visual field (2,3). Fortunately, treatment of patients with IIH improves visual function in at least half of patients (1).

Weight loss and oral medications, including acetazolamide, topiramate, and furosemide, are initial therapies for IIH if the disease is mild (1). When visual compromise is severe or if medical management is insufficient, surgical options include optic nerve sheath fenestration (ONSF) and cerebrospinal fluid (CSF) shunting (CSF diversion). Uncontrolled studies of ONSF and CSF shunting suggest that these procedures are effective in restoring visual function and improving symptoms of IIH, although neither is always effective and both can result in treatment failures (4–6) or adverse outcomes (7).

In some centers, CSF shunting procedures have become mainstays in the surgical treatment of IIH. Most commonly used are ventriculoperitoneal (VP) and lumboperitoneal (LP) shunts. Retrospective studies suggest that these procedures can result in improvement of the visual field (with kinetic perimetry) (8) and lessen symptoms of headache in some cases (9).

There are no case series of automated perimetry outcomes after CSF shunting in IIH patients. Our goal was to measure these outcomes in this patient population using the perimetric mean deviation (MD). Additionally, we studied Frisen papilledema grade and measurement of the average thickness of retinal nerve fiber layer (RNFL) by optical coherence tomography (OCT) to assess for changes in papilledema related to CSF shunting (10).
METHODS

A retrospective chart review was performed at the University of California Davis Eye Center to include all patients with the diagnoses of IIH and CSF shunting between 2004 and 2011. On review, we were able to identify 34 patients whose records included a diagnosis of IIH and CSF shunting. Of these 34 patients, 15 fulfilled the Modified Dandy Criteria for IIH, had documented papilledema, had a shunt placed to treat IIH, and were included in the study. These patients underwent surgery if they experienced persistent headache and/or progressive vision loss despite maximal medical therapy and weight loss recommendations. The timing of the surgery was variable depending on the severity of signs and symptoms.

All patients were required to have undergone automated perimetry, either full threshold or SITA 24-2 or 30-2, at baseline before the shunt placement, and the same visual field testing method was repeated after surgery.

Mixed effects regression models were fit to compare presurgical and postsurgical MD, average RNFL thickness measurement, and Frisen grade, controlling for differences due to age and sex, using the SAS software version 9.3 (SAS Institute, Cary, NC) procedures GLIMMIX (Frisen grade) and MIXED (MD, average RNFL thickness measurement). Standard linear or logistic regression models cannot be used for data with multiple measurements per subject because it violates the assumption of independence that standard regression models require. Mixed effects models control for intrasubject variability (differences between the eyes within a subject) and hence allow for repeated measurements on a subject (11).

RESULTS

Fifteen patients met entrance criteria. Fourteen of the patients were female and 1 was male. The ages ranged from 16 to 66 years, and the average age was 34 ± 12.7 years. Two of the patients underwent LP shunting, and 13 had VP shunting. Of the 15 patients, 4 underwent revisions of pre-existing shunts. Perimetry was performed between 0 and 7 months before the surgical intervention and between 2 and 17 months after surgery. Cirrus or Stratus OCT was obtained in 14 of the 15 patients preoperatively and in all 15 patients postoperatively. The same OCT device was used consistently in each patient. Fundus photography was obtained preoperatively in all 15 patients and in 13 of the patients postoperatively. A masked observer (M.W.) performed Frisen grading (12).

An example of patient testing results is shown in the Figure 1, which demonstrates the preoperative and postoperative fundus photos, automated visual fields, and optical coherence tomography (OCT) measurement of the average retinal nerve fiber layer (RNFL) thickness are shown. OD, right eye; OS, left eye.

Mean Deviation
Average preoperative MD was $-11.03 \pm 9.53$ dB, and average postoperative MD was $-5.40 \pm 7.16$ dB, yielding a difference of $5.63 \pm 1.19$ dB ($P < 0.0001$). All 15 patients (100%) had improved MD postoperatively in both eyes.

Retinal Nerve Fiber Layer
The preoperative average RNFL thickness measured $184.32 \pm 93.63$ μm. Postoperatively, the average RNFL thickness measured $97.05 \pm 23.59$ μm. The average RNFL thickness measurement was significantly smaller in postoperative measurements compared with preoperative ($P < 0.0001$). The average RNFL decreased by $87.27 \pm 16.65$ μm after surgery. Of the 14 patients with RNFL thickness data, 11 patients (78.57%) improved in both eyes, 2 patients (14.29%) improved in 1 eye but worsened in the other, and 1 patient (7.14%) worsened in both eyes.

Frisen Papilledema Grade
The average preoperative Frisen grade was $2.46 \pm 1.50$. The average postoperative Frisen grade was $0.27 \pm 0.44$. The average Frisen grade was significantly smaller postoperative measurements compared with preoperative ($P < 0.0001$).
DISCUSSION

While IIH patients with minimal or no visual loss can be managed conservatively with weight loss, if visual failure develops medical or surgical treatments are used (1,4). There are 2 main surgical options that may be offered to patients. ONSF has been shown to improve or stabilize visual function in approximately 90% of cases of IIH in retrospective case series (13–15). About 10% of these patients continue to worsen despite ONSF (5,16,17).

CSF shunting procedures also may be used for treatment of IIH. Both VP and LP shunting have resulted in improvement or stabilization of visual function in about 90% of cases in retrospective case series (5,6). However, despite treatment success with shunting, shunt failures occur frequently in greater than 50% of LP shunts (5,7) and approximately 30%–40% of VP shunts (5,6). Shunt failure can have significant consequences, such as acute rises in intracranial pressure that may result in severe and rapid visual loss with worsening papilledema (8). Additionally, the longer-term outcomes of CSF shunting are unclear regarding visual function.

Few previous studies of CSF shunting for IIH patients have reported visual field data. In one report of the efficacy of LP shunting, patients underwent static or kinetic perimetry, with improvement in static perimetry defined as at least 1 dB of improvement in MD (6). Another study evaluating the role of LP shunting used kinetic perimetry exclusively (8). A study of VP shunting for IIH included assessment with visual field function but did not report the type of perimetry or criteria defining improvement (5). A recent report of visual acuity and shunt survival in patients with LP shunting included results of automated perimetry, and MD was a secondary outcome measure (18).

We are unaware of any previous studies analyzing the quantitative effect of CSF shunting on perimetry results. Our study analyzed preoperative and postoperative outcomes and demonstrated that patients treated medically and with CSF diversion procedures had improved MD.

Our OCT data showed that the average RNFL thickness is also reduced by surgical intervention resulting in a reduction of the average RNFL thickness. As reported by Rebolleda and Munoz-Negrte (19) changes in RNFL in cases of mild papilledema are associated with visual field sensitivity losses and that sensitivity increased with resolution of papilledema. However, they also noted that the decreasing RNFL volume may also be due to loss of axons with resulting optic atrophy.

Additionally, our Frisen grading data demonstrate that CSF shunting results in an improvement in disc appearance in both eyes in most patients. Frisen grading was also used in the Neuro-Ophthalmology Research Disease Investigator Consortium Idiopathic Intracranial Hypertension Treatment Trial to evaluate 6 months of acetazolamide and diet for mild visual loss in IIH. Significant improvements in Frisen grade in both the study eye and the fellow eye were noted in fundus photographs and site investigator ratings (20). Although Frisen grading is subjective and dependent on experience, a study by Scott et al (21) reported good correlation between Frisen grading of optic nerve photographs and OCT analysis of optic nerves. In their study, Frisen grading was also bound to be more reliable than OCT at higher grades of papilledema.

Limitations of our study include the time gaps between preoperative evaluation, surgery, and postoperative testing. Although only the data most proximate to surgical intervention were included, it is possible that there were other causes of change in visual function. Additionally, both 24-2 and 30-2 visual field protocols were used so that comparison of the MD between patients cannot be compared exactly. Although some patients had multiple visual fields before surgery, others had this performed only when clinical deterioration was seen.
once, and this may have resulted in preoperative visual field measurements that overestimated the severity of the condition (22). It is possible that patients presenting with severe acute visual field loss may have been excluded from the study because of a lack of preoperative data. Patients with profound visual loss may not have had visual function measureable with perimetry, or they may have gone quickly to surgery without perimetry. Therefore, our patient population may be skewed toward those with less severe visual loss.

The results of our retrospective study suggest that CSF shunting may be an effective treatment for IIH. Long-term prospective studies are required to further explore the effects of CSF shunting regarding visual function. Comparison of CSF shunting with ONSF, as well as outcomes after shunt failures, also require further investigation.

REFERENCES

Evidence of Multidomain Mild Cognitive Impairment in Idiopathic Intracranial Hypertension

Dinah Zur, MD, Elvira Naftaliev, MD, Anat Kesler, MD

Background: Idiopathic intracranial hypertension (IIH), a disorder of unknown etiology, may occur in all age groups, but is most common in young obese women. Goals of treatment are to preserve vision and alleviate symptoms, including intractable headache, pulsatile tinnitus, and nausea. Cognitive function is not addressed routinely during clinical evaluation of IIH patients. The aim of our study was to test whether there is cognitive impairment in IIH patients and to evaluate the nature and characteristics of cognitive functions.

Methods: Design—Prospective cross-sectional observational study; Setting—Institutional; Study population—Thirty consecutive IIH patients (3 men and 27 women), mean age at time of testing was 34.4 years; Procedures—All participants completed a cognitive test battery; Outcome measures—Impairment of non-verbal memory, executive function, visual spatial processing, attention, motor skills, problem solving, and information processing speed in IIH patients.

Results: Mean scores for all domain index scores were below average for age and education. The global cognitive score, attention, and visual spatial indices had the lowest scores.

Conclusions: Our results indicate that patients with IIH have mild cognitive impairment. All domain measures apart from memory showed a statistically significant difference from normal individuals, indicating that there is a form of multidomain cognitive impairment in IIH. The relationship between cognitive impairment and chronically elevated intracranial pressures and its role in contributing to patient morbidity requires further study.

METHODS

Subjects

Participants were recruited from the Neuroophthalmology Unit, at the Tel Aviv Medical Center, Tel Aviv, Israel. Thirty consecutive adult male and female patients diagnosed with IIH scheduled for routine clinical follow-up were offered to participate in this prospective study. Patients in the acute phase of the disease were not enrolled; the time of diagnosis or of a relapse had to be at least 2 months before cognitive testing. Patients with history of a major psychiatric disorder, major depression, any neurological disorder except IIH or use of psychotropic drugs were excluded.
Testing Procedure

All participants completed a NeuroTrax battery of tests for mild cognitive impairment, which uses custom software installed on the testing computer (10).

The computerized battery of tests used in this study (testing time: 30 minutes) sampled non-verbal memory, executive function, visual spatial processing, attention, motor skills, problem solving, and information processing speed. Outcome parameters for tests or test levels included accuracy, reaction time (RT), standard deviation (SD) of RT, and a composite score ([accuracy/RT] × 100). Normalized subsets of outcome parameters were averaged to produce 7 summary scores. The outcome parameters contributing to each index score were included. The Global Cognitive Score (GCS) was computed as the average of the index scores. NeuroTrax index scores and GCS, computed using the same methodology, have been used in other studies (11–13).

The test results of the participants were compared with normative data in the NeuroTrax database. The normative sample is stratified according to age and education, and normalization of patient scores is according to the appropriate stratification. Normalization occurs automatically with upload of the test results to the NeuroTrax server. All individuals in the normative sample were tested in their primary language and diagnosed as cognitively healthy—as diagnosed by experienced clinicians as part of academic research studies using MindStreams performed at a variety of research sites (14–17).

The following are brief descriptions of the NeuroTrax tests included in our study.

Non-Verbal Memory
Eight pictures of simple geometric objects were presented, followed by a recognition test, in which 4 versions of each object were presented, each oriented in a different direction (Fig. 1A). Participants were required to remember the orientations of the originally presented objects.

Go–No Go Test
A series of large colored stimuli were presented at pseudorandom intervals (Fig. 1B). Participants were instructed to respond as quickly as possible by pressing a mouse button if the color of the stimulus was any color except red, for which no response was made.

Stroop Interference
The Stroop is a well-established test of response inhibition (18) (Fig. 1C). The NeuroTrax Stroop test consists of 3 phases. Participants were presented with a pair of large colored squares, one on the left and the other on the right side of the screen. In each phase, the participants were instructed to choose as quickly as possible which of the 2 squares was a particular color by pressing either the left or right mouse button, depending on which of the 2 squares is the correct color.

Visual Spatial Processing
Computer-generated scenes containing a red pillar were presented (Fig. 1D). Participants were instructed to imagine viewing the scene from the vantage point of the red pillar. Four alternative views of the scene were shown as choices.

Staged Information Processing Speed
This test comprises 3 levels of information processing load: single digits, 2-digit arithmetic problems (e.g., 5–1), and 3-digit arithmetic problems (e.g., 3+2–1). For each of the 3 levels, stimuli were presented at 3 different fixed rates, incrementally increasing as testing continues. Participants were instructed to respond as quickly as possible by pressing the left mouse button if the digit or result was less than or equal to 4 and the right mouse button if it was greater than 4.

“Catch” Game
The Catch game is a motor screen assessing cognitive domains distinct from those in other NeuroTrax tests (Fig. 1E). Participants had to “catch” a rectangular white object falling vertically from the top of the screen before it reached the bottom of the screen. Pressing on the mouse button moved a rectangular green “paddle” horizontally so that it could be positioned directly in the path of the falling object. The test required hand–eye coordination, scanning, and rapid responses.

Problem Solving
Pictorial puzzles of gradually increasing difficulty were presented (Fig. 1F). Each puzzle consisted of a 2 × 2 array containing 3 black and white line drawings and a missing element. Participants had to choose the best fit for the fourth (missing) element of the puzzle from among 6 possible alternatives.

NeuroTrax Summary Measures
To minimize differences in age and education and to permit averaging performance across different types of outcome parameters (e.g., accuracy, RT), each NeuroTrax outcome parameter was normalized and fitted to an IQ-style scale (mean: 100, SD: 15) in an age- and education-specific fashion. Normative data consisted of test data stored on the NeuroTrax central server for individuals classified as cognitively healthy in controlled clinical trials conducted at academic centers. Normalized subsets of outcome parameters were averaged to produce 7 summary scores as follows, each indexing a different cognitive domain.

Data Analysis
All statistics were computed with SPSS statistical package version 15.0. Neurocognitive test scores were converted into z-scores and compared with 0 (i.e., average)
using a one-sample t test to evaluate whether performance differed from average for age and education. An independent sample t test was run comparing treated patients with non-treated. Pearson correlations were used to evaluate the relationship of neurocognitive test scores with years of education and duration of disease. Statistical analysis was performed by the Statistical Laboratory School of Mathematics, Tel Aviv University, Tel Aviv, Israel.

Standard Protocol Approvals and Patient Consent
This prospective study was approved by the local institutional review board. Written informed consent was obtained from all patients participating in the study.

RESULTS

Participants
Thirty consecutive IIH patients participated, 3 men and 27 women. Mean age at the time of testing was 34.4 ± 10.6 years (range, 19–68 years). Mean disease duration was 5.7 ± 4.1 years. Body mass index (BMI) was available for 27 patients; mean BMI was 32.1 ± 5.8 kg/m². At the time of testing, all patients were at least 2 months from diagnosis, a relapse or a lumbar puncture. Eight patients were being treated with acetazolamide; 22 patients did not receive treatment to lower intracranial pressure (ICP). None of the patients had persistent impairment of visual acuity or visual fields. Mean years of education was 14.2 ± 2.0. Demographic data are shown in Table E1, Supplemental Digital Content, http://links.lww.com/WNO/A118. All patients denied suffering from severe or chronic headache when they were included in the study.

When informed consent was obtained from the participants, the test supervisor explained the objective of the study. As part of the pre-study screening, all 30 patients confirmed that they had noticed some cognitive decline after having been diagnosed with IIH. However, they had not mentioned it to the treating physician, as they attributed it to daily circumstances of life rather than IIH. None of our patients took medication for anxiety or depression and none of them complained about an anxiety state or disturbances of sleep, depressed mood, lack of appetite, loss of weight, or other signs of depression. None of the patients suffered from sleep apnea.

Domain Measures
Mean scores for all domain index scores were below average for age and education (See Supplemental Digital Content, Table E2, http://links.lww.com/WNO/A119 and Fig. 2). The GCS, attention, and visual spatial indices had the lowest scores with −0.63 to −0.73 SDs below average. A t test showed statistically significant differences from average for all domains but memory, which did not reach statistical significance (P = 0.162). The GCS and attention index were most impaired (P = 0.01). Results of all domains are shown in Table E3, Supplemental Digital Content, http://links.lww.com/WNO/A120.

Results did not differ between patients who did or did not take acetazolamide at the time of testing (for Global

DISCUSSION

Our results indicate that patients with IIH have mild cognitive impairment. All domain measures apart from memory showed a statistically significant difference from normal individuals, indicating a form of multidomain cognitive impairment in IIH.

Study of cognition in IIH patients is limited (6,8,9,12). Kharkar et al (8) reported retrospective results of 10 IIH patients and, similar to our results, found borderline deficits in memory, learning, executive function, and visuospatial skills and language were impaired. Yri et al (9) evaluated patients within 7 days of diagnosis of IIH, who were tested the second time after 3 months of treatment. Similar to our results, they found a multidomain impairment. Processing speed and RT were most profoundly impaired. In the study of Yri et al, attention scores and visuospatial memory improved at follow-up, whereas the others stayed unchanged. This improvement was mainly explained by the test–retest effect. Our results also support Yri’s findings, which showed no overall deficits in working memory, both in the acute and treated phase. Remarkably, Yri et al did not find a correlation between change in cognitive performance and difference in ICP from baseline. Arseni et al (19) found impaired memory in 24% of 85 IIH patients when tested with the Wechsler Memory Scale. Details of the nature and degree of memory impairment were not described nor were other cognitive functions measured. Sørensen et al (6) reported normal neuropsychological test performance in 5 IIH patients with a protracted clinical course.

In a prospective study of 20 IIH patients, 10 with chronic headaches and 9 healthy controls, Kesler et al (20) used brief psychological instruments to assess hostility (8-item New-Buss scale), anxiety (State-Trait Anxiety Inventory), and depression (autobiographical memory test). Patients with IIH scored higher on anxiety and showed reduced recall of specific autobiographical memories compared with weight-matched controls. No difference was found within the IIH group between patients taking or not taking acetazolamide.

Information regarding QoL and cognitive functions in IIH patients is limited: The impact of IIH on health-related QoL has been studied by Kleinschmidt et al (3) who reported a higher incidence of depression and anxiety in IIH patients compared with weight- and age-matched control groups. Vision-specific health-related QoL was significantly lower in newly diagnosed IIH patients compared with neuro-ophthalmologic controls. Kesler et al (5) found high levels of anxiety and stress in IIH patients. Depression and anxiety themselves are known to cause cognitive decline, impairing memory, executive functions, and learning (21). Accordingly, Airaksinen et al (22) found significant impairment in episodic memory and executive functions in anxious patients.

The relationship between IIH and cognitive impairment is unclear. Neither structural change nor change in brain volume has been identified in IIH patients. Brain dysfunction may be related to axonal flow as in optic nerve swelling or to mechanical compression as in normal pressure hydrocephalus (23,24).

We speculated that elevated ICP may cause diffuse effects in a broad array of brain areas. We found poorer performance in all cognitive domains tested. Attention and visual spatial processing scores were lowest. Even though memory was below average, it did not reach statistical significance. Our results demonstrated that cognitive decline was not related to patient age, disease duration, BMI, or acetazolamide treatment. The absence of correlation with these other variables implicates that IIH itself may cause cognitive impairment.

A limitation of our study is that we did not test patients for anxiety and depression, although none of the participants had a diagnosis of a psychiatric disorder. Yet, it is well known that anxious and depressive disorders are often unrecognized in the population. Hence, there may be a portion of patients that suffered from undiagnosed anxiety or depression and a possible impact on cognitive results cannot be ruled out.
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Statistical analysis was performed by the Statistical Laboratory School of Mathematics, Tel Aviv University, Tel Aviv, Israel.

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Asymmetric Papilledema in Idiopathic Intracranial Hypertension

Samuel Bidot, MD, Beau B. Bruce, MD, PhD, Amit M. Saindane, MD, Nancy J. Newman, MD, Valérie Biousse, MD

Background: Very asymmetric papilledema in idiopathic intracranial hypertension (IIH) is rare, and few studies have dealt with this atypical presentation of IIH. Our aim was to describe the clinical and radiologic features of patients with IIH and very asymmetric papilledema.

Methods: We identified all adult patients from our IIH database with very asymmetric papilledema defined as a \( \geq 2 \) modified Frisén grade difference between the 2 eyes. Demographic data and initial symptoms were collected, and all brain imaging studies performed at our institution were reviewed.

Results: Of the 559 adult patients with definite IIH, 20 (3.6%; 95% confidence interval [CI], 2.3–5.6) had very asymmetric papilledema at initial evaluation. They were older (39 vs 30 years; \( P < 0.001 \)), had lower cerebrospinal opening pressure (35.5 vs 36 cm of water; \( P = 0.03 \)), and were more likely to be asymptomatic compared with patients with symmetric papilledema (27% vs 3%; \( P < 0.001 \)). Visual fields were worse on the side of the highest-grade papilledema (\( P = 0.02 \)). The bony optic canal was smaller on the side of the lowest-grade edema in all 8 patients (100%) in whom the imaging was sufficient for reliable measurements (\( P = 0.008 \)).

Conclusions: IIH with very asymmetric papilledema is uncommon. Very asymmetric papilledema may result from differences in size of the bony optic canals, supporting the concept of compartmentation of the perioptic subarachnoid spaces.

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Very asymmetric papilledema in idiopathic intracranial hypertension (IIH) is an uncommon finding that can raise concern for alternate diagnoses, such as unilateral optic neuropathy. Few studies have systematically addressed the issue of asymmetric papilledema in IIH, and most are only case reports or small case series (1–11). The largest series of 38 patients focused specifically on visual function outcome (12), and only 1 study has detailed orbital imaging findings (13). Very asymmetric papilledema offers a unique opportunity to study factors proposed in the pathogenesis of papilledema. Although several mechanisms have been suggested to explain very asymmetric papilledema, such as optic nerve sheath defects and loss of lamina cribrosa compliance (1,6), its mechanism remains unclear.

Our aim was to describe the clinical and radiologic features of patients with IIH and very asymmetric papilledema and to characterize factors associated with this unusual presentation of IIH.

METHODS

Clinical Evaluation

Our study was approved by the Emory University Institutional Review Board. Using our established database of patients seen in our center between 1989 and 2013, we identified all adult patients (age 18 years or older) with definite IIH according to the modified Dandy criteria (14). Although this study was a retrospective chart review, all patients were evaluated in a standardized fashion, and all had fundus photographs at presentation.
We first selected all patients with IIH from our IIH database, who had been recorded as having a ≥1 Frisén grade difference in papilledema between the 2 eyes at initial presentation. All fundus photographs were then unpaired and graded independently using the modified Frisén scale (15) in random order by 2 neuro-ophthalmologists (S.B. and B.B.B.), who were masked to the patients’ clinical data. In case of disagreement, the third neuro-ophthalmologist (V.B.) was asked to grade the papilledema. We defined very asymmetric papilledema as a ≥2 modified Frisén grade difference between the 2 eyes and selected all patients with IIH with at least 2 grades of difference in their papilledema.

Demographic data of all patients with very asymmetric papilledema including age, gender, body mass index (BMI), and race were collected. Initial symptoms (visual loss, transient visual obscurations, diplopia, tinnitus, and headaches), Snellen visual acuity, intraocular pressure (IOP), automated visual field, and visual fields were recorded. The presence or absence and side of transverse sinus stenosis was evaluated from either the contrast-enhanced MRV, postcontrast T1 (16), 2D TOF MRI, postcontrast CT, or transverse sinus flow voids on T2 images when there was no contrast-enhanced image set. When possible, and before recording the radiologic findings, cross-sectional area of both the right and left optic canals were measured using either precontrast T1 volumetric 1 mm isotropic area, by reformating into a coronal oblique plane orthogonal to the axis of each optic canal, or thin-section CT examination that was also reformatted in a similar fashion using images of 0.625 mm to obtain cross-sectional area (Fig. 1).

**Statistical Analysis**

All statistical analyses were performed with R: A language and environment for statistical computing (R Foundation for Statistical Computing, http://www.R-project.org). Continuous and ordinal variables were compared between groups using the Mann–Whitney U test. Pearson χ² with Yates continuity correction or Fisher exact test, as appropriate, were used to compare categorical variables. The eyes of patients with very asymmetric papilledema were compared using the Wilcoxon signed rank test for continuous variables and paired proportion test for categorical variables. These tests were 2 tailed, and significance was set at 5%.

**RESULTS**

Of the 559 adult patients with definite IIH seen over 24 years, 20 (3.6%; 95% confidence interval [CI], 2.3–5.6) had very asymmetric papilledema defined as a ≥2 modified Frisén grade difference between the 2 eyes at initial evaluation. Patients with very asymmetric papilledema were significantly older (39 vs 30 years; \( P < 0.001 \)), had significantly lower CSF OP (35.5 vs 36 cm of water; \( P = 0.03 \)), and were significantly more likely to be asymptomatic compared with patients with more symmetric papilledema (27% vs 3%; \( P < 0.001 \)) (Table 1).

The highest-grade edema was on the right side in 9 of 20 patients (45%). Papilledema was strictly unilateral in 8 of 20 patients (40%) and was located on the right side in 3 of 8 patients (38%). When comparing the eye with the highest-grade edema to the fellow eye, visual fields were significantly worse (mean deviation, −3.0 vs −2.1 dB; \( P = 0.02 \)), but visual acuities and IOPs were not different (Table 2).

Neuro-imaging (11 MRIs and 1 CT) was performed at our institution for 12 of 20 patients. Nine of 11 patients with MRI received intravenous gadolinium contrast material, and 3 of 11 patients had an MRV (contrast-enhanced MRV: 2/3 patients). The optic canal was smaller on the side of the lowest-grade edema in all 8 patients (100%, 7 MRIs and 1 CT) in whom it could be reliably evaluated (Table 2). The cross-sectional optic canal measurement was 14.9% smaller on average on the side of the lowest-grade edema
FIG. 1. Cross-sectional area measurement technique. Figures on the right and left match with the right and left side, respectively. Figures (A–C) come from the same patient, and measurement was obtained by using precontrast T1 volumetric MRI (B and C). Figure (D) come from another patient to illustrate the technique using thin-section CT scan reconstruction. A. Optic disc appearance. Asymmetric papilledema, grade 2 in the right eye and grade 4 in the left eye. B. Positioning of the guides in the axial plane. Measurement of the cross-sectional area of each optic canal using MRI (C) and CT (D). CT, computed tomography; MRI, magnetic resonance imaging.
Asymmetric peri-optic nerve CSF was reported in 6 of 12 patients (50%) and was always less prominent on the side of the lowest-grade edema ($P = 0.01$). Optic nerve protrusion into the globe and scleral flattening, both trended toward being more common on the side of the highest-grade edema ($P = 0.07$).

**DISCUSSION**

Our study confirms that very asymmetric papilledema is rare in IIH, occurring in less than 4% of patients with definite IIH. Interestingly, we showed that the bony optic canal was always smaller on the side of the lowest-grade edema.

Few reports (1–13) have dealt with asymmetric papilledema in IIH. Three studies reported its prevalence in a tertiary neuro-ophthalmic setting (1,11,12), and found heterogeneous results. Using the same definition of asymmetric papilledema, Wall and White (12) and the Idiopathic Intracranial Hypertension Treatment Trial (11) have shown that IIH with very asymmetric papilledema was uncommon ($\approx 7.5\%$), but a smaller series of 6 patients (1) found a higher prevalence (23%). Surprisingly, our study found a much lower prevalence of 3.6%. Several factors may have contributed to these discrepancies. First, we believe that the high prevalence found by Lepore (1) should be interpreted cautiously because the sample was...
small (6/27 patients; 95% CI, 7.1–38.9) and no details regarding the definition of asymmetric papilledema were provided. Second, we had a strict definition of very asymmetric papilledema to emphasize the potential differences between symmetric and asymmetric papilledema in terms of demographics, clinical presentation, and radiologic features; therefore, we might have underestimated its prevalence.

Regarding patient demographics, we found that patients with IIH with very asymmetric papilledema were older compared with patients without asymmetric papilledema, which also was reported by Lepore (1). Lepore (1) suggested a possible loss of compliance in the aging lamina cribrosa, buffering the effect of the perioptic CSF pressure. However, he did not address how this would result in asymmetric papilledema. Wall and White (12) found an overrepresentation of men (29%); we also found a higher frequency of men (15%) among patients with very asymmetric papilledema, but this did not reach significance when compared with the group of patients with symmetric papilledema. In our study, race and BMI of patients with very asymmetric papilledema were similar to those with symmetric papilledema.

The clinical presentation of patients with IIH with very asymmetric papilledema seems to differ from that of patients with IIH with symmetric papilledema, with a high proportion of asymptomatic cases (27%) and a lower proportion of patients with headaches (35%) in the asymmetric papilledema group. In a previous series including patients from the same IIH database (17), we emphasized that men with IIH experience headache less often. Our higher frequency of men with very asymmetric papilledema, none of whom had headache, may account partially for this difference. In addition, although no correlation between headaches and CSF OP in IIH has been reported, the significantly lower CSF OP we found among patients with very asymmetric papilledema might have contributed to the difference in headache frequency. Regarding visual function, as previously reported (12), visual fields were significantly worse on the side of the highest-grade papilledema.

The most interesting result from our study is that the bony optic canals were consistently smaller on the side of the lowest-grade papilledema. The pathophysiology of CSF dynamics in IIH is not fully understood (18). The lack of a clear relationship between the degree of papilledema and the CSF OP (14,19) suggests that an underlying mechanism may sometimes prevent the optic disc from swelling in some cases of IIH. The pathogenesis of papilledema depends on the transmamellar pressure gradient at the optic nerve head, and therefore on the balance between the CSF pressure in the perioptic subarachnoid spaces and the IOP. Hayreh (20) showed that high CSF pressure in the perioptic subarachnoid spaces or low IOP cause identical microscopic changes and axonal flow stasis. However, our study and others (2,7,13) have shown that asymmetric IOP, although reported in anecdotal cases (3,5,10), is not the primary mechanism of asymmetric papilledema. We believe that, in the absence of optic atrophy (20), asymmetric papilledema is most likely related to asymmetric transmission of the CSF pressure to the lamina cribrosa (21).

Two mechanisms for asymmetric transmission of the CSF pressure along the perioptic subarachnoid spaces previously have been proposed, namely asymmetric structural changes either in the lamina cribrosa (1) or along the optic nerve sheath (6). These mechanisms remain debated. Our study shows compelling data regarding the role of asymmetry of the bony optic canals in the genesis of very asymmetric papilledema. It is well known that the orbital portion of the perioptic subarachnoid spaces shows distension in IIH (22,23). A study of 15 patients with IIH, 10 with IIH, failed to demonstrate asymmetric distension of the perioptic subarachnoid spaces in patients with unilateral papilledema, but no details regarding the grading of papilledema were provided (13). We included only very asymmetric papilledema to identify obvious potential differences between the 2 eyes. We showed that asymmetric distension of the perioptic subarachnoid spaces occurred in half of our cases, always less prominent on the side of the lowest-grade edema, suggesting that the CSF pressure may be lower in the perioptic subarachnoid spaces on the side of the lowest-grade edema. Possibly, our imaging or grading system might not have been sensitive enough to capture subtle asymmetry in the remaining 50% of cases with symmetric perioptic CSF.

The concept of compartmentation of the perioptic subarachnoid spaces (4,24,25), in which the perioptic subarachnoid spaces are partially separated from the suprasellar cisternal spaces, seems more likely to explain asymmetric papilledema. Although the orbital portion of the perioptic subarachnoid spaces is able to distend under increased CSF pressure, the intracanalicular portion, the narrowest (4,19), is characterized by tight relationships between the surrounding bone and the optic nerve (24). Because of its unique anatomy, the region of the optic canal plays a crucial role in CSF flow dynamics between the suprasellar cistern and the perioptic subarachnoid spaces. We have demonstrated that the bony optic canal was always smaller on the side of the lowest-grade edema. This anatomic configuration probably allows CSF pressure to be less easily transmitted along the optic nerve on the side of the smaller canal, thereby resulting in lower local intraorbital CSF pressure and less optic disc edema. However, longitudinal data on the optic canal diameter in patients with IIH are needed to better understand whether this asymmetry in size is congenital or results from bony erosion related to longstanding CSF hypertension, as described in other skull base locations with chronic IIH (26,27). The fact that we and others (1) have found that patients with IIH with asymmetric papilledema are older than other patients with IIH may support an acquired etiology.

Despite our small sample, there seems to be a definite relationship between the severity of papilledema and the cross-sectional area of the optic canal, suggesting that asymmetric papilledema may result from asymmetries in

the bony optic canal. Our study lends further support to the concept of compartmentation of the perioptic subarachnoid spaces developed by Killer and Subramanian (24) and suggests that the bony optic canal may be a “bottleneck” interfering with the CSF flow between the perioptic subarachnoid spaces and the suprasellar cistern. Whether the asymmetry in size of the optic canal is congenital or acquired requires further study.

STATEMENT OF AUTHORSHIP

REFERENCES
Risk Factors and Prognosis of Isolated Ischemic Third, Fourth, or Sixth Cranial Nerve Palsies in the Korean Population

Ji Sung Jung, MD, Dae Hyun Kim, MD, PhD

Background: To investigate the risk factors and prognosis for ischemic third, fourth, and sixth cranial nerve palsies in a Korean population.

Methods: A pair-matched case–control study of 54 Korean patients who were diagnosed with ischemic third, fourth, or sixth cranial nerve palsies was performed to evaluate their risk factors. Using conditional logistic regression analysis, prevalence of potential risk factors in patients and controls, included diabetes mellitus, hypertension, hyperlipidemia, ischemic heart disease, left ventricular hypertrophy (LVH), and smoking were examined retrospectively. A cohort study by Kaplan–Meier method was performed to analyze the recovery period in relation to the number of risk factors or intracranial abnormalities detected by brain computed tomography or magnetic resonance imaging.

Results: The mean age of onset was 64.5 years. Of the 54 patients, 16 (29.6%) developed a third nerve palsy, 19 (35.2%) a fourth nerve palsy, and 19 (35.2%) a sixth nerve palsy. The risk factors of diabetes mellitus, hypertension, and hyperlipidemia were significantly more prevalent than other risk factors of heart disease, LVH, and smoking. The mean number of risk factors was 2.3 ± 0.6 in the third nerve palsy group, 1.7 ± 0.9 in the fourth nerve palsy group, and 1.6 ± 1.0 in the sixth nerve palsy group. Patients with 2 or more risk factors showed a longer recovery period (9.0 ± 5.1 weeks) than did patients who had 1 risk factor (6.1 ± 2.2 weeks). Patients with intracranial abnormalities on neuroimaging showed a longer recovery time (10.4 ± 2.7 weeks) than did those without intracranial abnormalities (7.5 ± 4.8 weeks).

Conclusions: Ischemic ocular motor cranial nerve palsy is closely related to diabetes mellitus, hypertension, and hyperlipidemia in Korean patients. Compared with the fourth or sixth nerve palsy groups, the third nerve palsy group showed a tendency to have multiple risk factors. Recovery takes longer when 2 or more risk factors were present or when abnormal findings were observed on neuroimaging.

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Previous studies have shown that ocular motor cranial nerve palsies have a variety of causes including vascular disease, head trauma, intracranial tumor or aneurysm, and inflammatory disorders (1–3). Systemic vascular disease, particularly diabetes mellitus and hypertension, lead to microvascular ischemia and are frequent causes of these acquired neuropathies (1–4). Other reported risk factors are advanced age, left ventricular hypertrophy (LVH), ischemic heart disease (IHD), increased hematocrit concentration, obesity, hyperlipidemia, and cigarette smoking (5–9).

To the best of our knowledge, most studies analyzing these risk factors were conducted in Western populations (5–8), and only one involved an Asian population (9). In our retrospective case–control study, we assessed risk factors for isolated, acute ischemic third, fourth, or sixth cranial nerve palsies and identified the factors affecting time to recovery in a Korean patient cohort.

PATIENTS AND METHODS

We retrospectively reviewed the medical records of 54 patients who complained of diplopia, blepharoptosis, or ocular motility disturbance and were diagnosed with acute, ischemic, isolated third, fourth, or sixth cranial nerve palsies. All patients were evaluated in the Ophthalmology Department of Chosum University from January 2009 to December 2013. Institutional Review Board approval was obtained at the Chosum University Hospital.

Inclusion criteria were (1) age greater than 50 years; (2) new onset of ocular motor cranial nerve palsy within 2 weeks of initial evaluation; (3) no history of trauma within
the preceding 3 months; and (4) no evidence of intracranial neoplasm, aneurysm, or inflammation on neuroimaging studies at the time of diagnosis or during follow-up. Patients with congenital etiologies or the presence of other neurological signs and symptoms, multiple cranial neuropathies, thyroid disease, multiple sclerosis, or myasthenia gravis were excluded. In the case of third nerve palsy, patients with pupil involvement were excluded, but patients with mild anisocoria up to 1.5 mm were included if there was no evidence of aneurysm or neoplasm on brain imaging.

Systemic risk factors were as follows. A diagnosis of hypertension was made if systolic pressure was $\geq 140$ mm Hg or diastolic pressure was $\geq 90$ mm Hg or if the patient was taking oral hypertensive medication as previously diagnosed with hypertension (10). Diabetes mellitus was defined when the patient was taking oral hypoglycemic drugs or insulin. Some individuals were newly diagnosed in the Department of Endocrinology. We assumed that individuals had hyperlipidemia if their random cholesterol level was $> 240$ mg/dL or if the patient was taking medications for cholesterol reduction (11). IHD was defined by electrocardiographic documentation of myocardial infarction or a history of taking antianginal medications. LVH was defined by its presence on electrocardiography or echocardiography (12,13). Patients who were active cigarette smokers at the time of diagnosis or had used tobacco in the previous 5 years were regarded as smokers (14,15).

Each patient had an initial neuro-ophthalmologic examination by one of the authors (D.H.K.) and underwent neuroimaging with magnetic resonance imaging (MRI) or computed tomography (CT). Patients were seen at 2-week intervals until diplopia resolved and ocular motility returned to normal. We reviewed the medical records retrospectively and documented the age at onset, gender, associated risk factors, and time until recovery.

We established a control group matched for age and gender selected randomly from a pool of individuals who received health examinations at the Chosun University Hospital Health Promotion Center during the same time period. The average number of accompanying risk factors was $1.8 \pm 0.9$ in the patient group. This result was significantly higher than the $0.9 \pm 1.0$ in the control group ($P < 0.001$). The percentage of those with 2 or more risk factors was significantly greater in the patient group ($n = 34, 63.0\%$) than in the control group ($n = 13, 24.1\%$ ($P < 0.001$). The most frequent combination of risk factors was hypertension and diabetes (9 patients, 26.5\%), followed by hypertension, diabetes, and LVH (4 patients, diabetes

### RESULTS

Among the 54 patients in this study, 16 showed third cranial nerve palsies (29.6\%), 19 showed fourth cranial nerve palsies (35.2\%), and 19 showed sixth cranial nerve palsies (35.2\%). Thirty-one of the patients (57.4\%) were male, and 23 (42.6\%) were female. The mean age was 64.5 ± 10.2 years, and 33 of the patients (61.1\%) were ≤60 years. The mean time from symptom onset to first examination was 9.8 ± 9.8 days, and the mean follow-up period was 37.6 ± 21.7 weeks.

The distribution of potential risk factors in the subject and control groups is shown in Table 1. In the patient group, 34 of the 54 patients (63.0\%) had hypertension, 29 (53.7\%) had diabetes mellitus, 13 (24.1\%) had hyperlipidemia, 4 (7.4\%) had IHD, 7 (13.0\%) had LVH, and 12 (22.2\%) were smokers. Diabetes mellitus was significantly more prevalent in the patient group than in the control group (OR of 9.57; 95\% CI, 3.23–28.35). Hyperlipidemia (OR of 3.92; 95\% CI, 1.09–14.12) and hypertension (OR of 2.73; 95\% CI, 1.02–7.29) were also significantly more frequent in the patient group. IHD, LVH, and smoking also were more common in the patient group, but the differences were not statistically different.

The odds ratios (ORs) with 95\% confidence intervals (CIs) of each risk factor were obtained by conditional logistic regression analysis to express the association of ischemic ocular motor nerve palsy and the potential risk factors. Paired t test was performed to compare the distribution of the number of vasculopathic risk factors in the patient group and the control group. The cohort study by Kaplan–Meier method was used to analyze recovery period in relation to the number of risk factors or intracranial abnormalities. Statistical analysis was performed with SPSS (version 19.0; Chicago, IL) and $P$-values < 0.05 were considered significant.

### TABLE 1. Distribution of risk factors for ischemic ocular motor nerve palsy group and control group

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Cases, N = 54 (%)</th>
<th>Controls, N = 54 (%)</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>34 (63.0)</td>
<td>20 (37.0)</td>
<td>2.731</td>
<td>1.023–7.287</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>29 (53.7)</td>
<td>6 (11.1)</td>
<td>9.573</td>
<td>3.233–28.350</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>13 (24.1)</td>
<td>5 (9.3)</td>
<td>3.917</td>
<td>1.087–14.121</td>
</tr>
<tr>
<td>IHD</td>
<td>4 (7.4)</td>
<td>3 (5.6)</td>
<td>1.360</td>
<td>0.290–6.388</td>
</tr>
<tr>
<td>LVH</td>
<td>7 (13.0)</td>
<td>4 (7.4)</td>
<td>1.862</td>
<td>0.172–3.795</td>
</tr>
<tr>
<td>Smoking</td>
<td>12 (22.2)</td>
<td>8 (14.8)</td>
<td>1.643</td>
<td>0.612–4.411</td>
</tr>
</tbody>
</table>

CI, confidence intervals; IHD, ischemic heart disease; LVH, left ventricular hypertrophy; OR, odds ratio.
TABLE 2. Distribution of patients with ischemic ocular motor cranial nerve palsy group by the summation of risk factors

<table>
<thead>
<tr>
<th></th>
<th>3rd Nerve (n = 16)</th>
<th>4th Nerve (n = 19)</th>
<th>6th Nerve (n = 19)</th>
<th>Total (n = 54)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 risk factor</td>
<td>1 (6.3%)</td>
<td>9 (47.4%)</td>
<td>10 (52.6%)</td>
<td>20 (37.0%)</td>
<td></td>
</tr>
<tr>
<td>2–3 risk factors</td>
<td>15 (93.8%)</td>
<td>10 (52.6%)</td>
<td>9 (47.4%)</td>
<td>34 (63.0%)</td>
<td>0.047*</td>
</tr>
<tr>
<td>Average number of accompanying risk factors</td>
<td>2.3 ± 0.6</td>
<td>1.7 ± 0.9</td>
<td>1.6 ± 1.0</td>
<td>1.8 ± 0.9</td>
<td>0.008*</td>
</tr>
</tbody>
</table>

*Kruskal–Wallis test among the each cranial palsy group by summation of risk factor.

and smoking (4 patients), and then by coexisting hypertension, diabetes, and hyperlipidemia (3 patients). Analyzing the average number of accompanying risk factors based on the affected nerve in the patient group, the third cranial nerve palsy group had 2.3 ± 0.5 risk factors compared with 1.7 ± 0.9 in the fourth nerve palsy and 1.6 ± 1.0 in the sixth nerve groups (P = 0.047) (Table 2).

In our study, 48 of the 54 patients (88.9%) underwent brain imaging studies, MRI in 44, and CT in 4. Eleven patients (22.9%) had incidental intracranial abnormalities in which the lesion was not directly related to the cause of the neuropathy, including 5 multiple lacunar infarctions, 2 old cerebellar infarctions, 2 old cerebral infarctions, and 2 stenosis of the internal carotid artery.

The mean duration to recovery of all 54 patients was 7.9 ± 4.4 weeks; 9.0 ± 6.6 weeks in the third nerve palsy group, 7.3 ± 2.9 weeks in the fourth nerve group, and 7.6 ± 3.4 weeks in the sixth nerve group (Table 3). Patients who had 2 or more risk factors showed a significantly longer recovery period (9.0 ± 5.1 weeks) than did patients who had 1 risk factor (6.1 ± 2.2 weeks) (P = 0.025). In addition, we observed that patients who showed abnormal brain imaging findings had a longer recovery period of 10.4 ± 2.7 weeks compared with patients who had no intracranial abnormalities at 7.5 ± 4.8 weeks (P = 0.008).

DISCUSSION

In this study involving Korean patients, the risk of developing an ocular motor cranial nerve palsy was 10 times higher in patients with diabetes than in non-diabetic control group. This is consistent with previous studies (3,5,6,16–18), which have shown the frequency of diabetes mellitus in patients with ischemic ocular motor neuropathies ranges from 36% to 48% (5,6,9). This is less than the 53.7% frequency found in our study. The difference in results may depend on the diagnostic criteria. For example, in our patients, we did not include blood glucose intolerance in establishing the diagnosis of diabetes.

In most studies, hypertension is significantly more common in patients with ischemic ocular motor cranial nerve palsy and identified as an important risk factor (1-3,5,19). However, after controlling for the other risk factors in the control group, Jacobson et al (6) determined that hypertension was not an independent risk factor. In a report of Japanese individuals, Kobaishi et al (9) found that hypertension was not present at an increased frequency when patients were compared with a control group. In this study of Korean subjects, hypertension was found to be present in 63% of the patient group, 3 times the frequency found in the control group, and was statistically significant. Jacobson et al (6) identified that LVH was an independent risk factor, but this was not the case in our patient cohort.

Increased cholesterol was a significant risk factor in our Korean patients, observed in 11 of the 54 subjects in the patient group (24%). Our findings are similar to the study performed in Japan (9), where 13 of the 46 patients (28%) had increased cholesterol, but lower than those found in the study by Jacobson et al (6), where 30 of 65 patients (46%) had increased blood cholesterol and not found to be an independent risk factor. Murchison et al (20) reported that 61 of 93 patients (65%) who had ischemic ocular motor cranial nerve palsy also had increased cholesterol level, but did not compare this with a control group.

Smoking increases vasoconstriction, platelet aggregation, and red and white blood cell counts and is known to increase the risk of stroke and IHD among patients with diabetes mellitus and hypertension. It also decreases high-density

TABLE 3. Recovery period of patients with ischemic ocular motor cranial nerve palsy

<table>
<thead>
<tr>
<th></th>
<th>3rd Nerve (n = 16)</th>
<th>4th Nerve (n = 19)</th>
<th>6th Nerve (n = 19)</th>
<th>Total (n = 54)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovery period, wk</td>
<td>9.0 ± 6.6</td>
<td>7.3 ± 2.9</td>
<td>7.6 ± 3.4</td>
<td>7.9 ± 4.4</td>
<td></td>
</tr>
<tr>
<td>1 risk factor</td>
<td>4.9 ± 0.0</td>
<td>5.9 ± 2.2</td>
<td>6.5 ± 2.4</td>
<td>6.1 ± 2.2</td>
<td>0.025*</td>
</tr>
<tr>
<td>2–3 risk factors</td>
<td>9.3 ± 6.8</td>
<td>8.7 ± 3.0</td>
<td>9.0 ± 3.9</td>
<td>9.0 ± 5.1</td>
<td></td>
</tr>
<tr>
<td>Intracranial abnormalities (+)</td>
<td>9.6 ± 1.1</td>
<td>12.1 ± 1.0</td>
<td>10.2 ± 4.9</td>
<td>10.4 ± 2.7</td>
<td>0.008*</td>
</tr>
<tr>
<td>Intracranial abnormalities (−)</td>
<td>9.0 ± 8.1</td>
<td>6.3 ± 2.4</td>
<td>7.4 ± 2.8</td>
<td>7.5 ± 4.8</td>
<td></td>
</tr>
</tbody>
</table>

*Kaplan–Meier method between the number of risk factors or intracranial abnormalities.
lipoprotein levels (21). The frequency of smoking in our study was 12 of 54 patients (22.2%), which was not an independent risk factor, similar to other reports (6,9).

We found that patients with ischemic third nerve palsy had vascular risk factors more frequently than patients with fourth or sixth nerve palsy. The reason for this finding is unclear.

We analyzed the factors that influence time to recovery in patients with ischemic ocular motor cranial nerve palsy. As in the study of Japanese patients (9), our results showed that recovery takes longer when more than 2 risk factors are present.

Patients who demonstrated intracranial abnormalities on neuroimaging had a longer recovery period. However, patients who showed abnormal findings on brain imaging had more than 2 risk factors, and it was difficult to identify whether these risk factors independently influenced the time to recovery. Of 54 patients, 48 underwent brain imaging and abnormal findings were detected in 11 (22.9%). The most frequent finding was multiple lacunar infarctions, observed in 5 patients. However, the findings did not have a causal relationship with ocular motor cranial nerve palsy.

In conclusion, diabetes mellitus, hypertension, and hyperlipidemia are independent risk factors for ischemic third, fourth, or sixth cranial nerve palsy. Patients with third nerve palsy tended to have multiple risk factors. Recovery took longer when many risk factors were present and when abnormal findings were observed on neuroimaging. This retrospective single hospital-based study along with a small patient sample size are the limitations in generalizing our results. Nevertheless, unlike previous reports of Western populations, this research provides information regarding ischemic ocular motor nerve palsies in an Asian population.

STATEMENT OF AUTHORSHIP

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Maffucci Syndrome and Intracranial Chondrosarcomas: A Case Report Featuring Spontaneous Resolution of Sixth Nerve Palsy

Monique Munro, MD, Fiona Costello, MD, FRCPC, David Burrowes, MD, Ryan Yau, MD, FRCSC

Abstract: Maffucci syndrome is a rare disease process characterized by enchondromatosis with cutaneous hemangiomatosis. We report a 20-year-old woman with Maffucci syndrome with a 5-day history of diplopia. She was found to have a left sixth nerve palsy due to a parasellar chondrosarcoma. Three weeks later, the patient’s diplopia spontaneously resolved. This unusual clinical course prompted us to review frequency of sixth nerve palsy with skull base neoplasms and the phenomenon of spontaneous resolution of diplopia.


Maffucci syndrome is a rare congenital mesenchymal dysplasia characterized by multiple enchondromas and subcutaneous hemangiomas (1–3) and first described by Angelo Maffucci in 1881. In a 2007 review, 209 cases of Maffucci syndrome had been documented in the literature (4). The cause of this syndrome remains unknown but seems to be nonhereditary, has no gender or racial predilection, and karyotypes are normal (2). The enchondromas develop asymmetrically from cartilaginous remnants in the physeal growth plates and predominantly affect long or flat bones (2–5). Patients tend to be severely affected with gross deformities and shortening of the extremities and are often diagnosed as children when bony development is most rapid (3). Clinical findings are typically present at birth or develop in the first year of life in 25% of patients and are seen in nearly 9% by puberty (4). Abnormal cartilaginous proliferation usually arrests when growth ceases and the main complication thereafter is sarcomatous degeneration of the enchondromas and development of systemic malignancies (3,5–7). The reported incidence of sarcomatous transformation of enchondromas is 15% (8). Systemic malignancies, predominantly ovarian, pancreatic, and central nervous system, have been reported in up to 25% of patients. Schwartz et al (9), using life-table analysis, calculated that 100% of patients will develop a malignancy in their lifetime, rendering close surveillance mandatory for all patients (1,3–5,8,10).

Among 200 reported cases of malignancies associated with Maffucci Syndrome, less than 10% were located in the skull base, and less than half of these were chondrosarcomas (10). Although chondrosarcomas frequently occur in patients with Maffucci syndrome, intracranial chondrosarcomas are rare, with only 15 cases of skull base chondrosarcomas reported in association with Maffucci syndrome (3–5,7,10–18).

Sixth nerve palsy is a frequent neuro-ophthalmic abnormality in patients with skull base chondrosarcomas (19). Yet, most progress due to mass effect and rarely demonstrate spontaneous improvement (3). We document such a case in a patient with Maffucci syndrome.

CASE REPORT

A 20-year-old woman reported a 5-day history of constant diplopia, which was worsening in severity. She had been diagnosed with Maffucci syndrome 6 years previously with manifestations including left forearm medial deviation, bony changes affecting the hands, and vascular masses of the left toes. She also had a history of ovarian cancer, which...
had been treated with oophorectomy and chemotherapy. Her ocular history was unremarkable.

At presentation, visual acuity was 20/20 bilaterally with normal pupillary findings. Ocular motility revealed limited abduction of the left eye and a 14 prism diopter esotropia in primary position. External examination was unremarkable without evidence of proptosis. Confrontational visual field testing was normal, and fundus examination was unremarkable. The remainder of the neurologic examination was within normal limits.

Brain magnetic resonance imaging disclosed a mass lesion centered within the left lateral wall of the sella, superior to the main portion of the clivus, and extending to the anterior and posterior clinoids with the dura displaced superiorly. The lesion measured approximately 16 mm in anteroposterior diameter by 17 mm in transverse diameter by 15 mm in the craniocaudal diameter (Fig. 1). Brain parenchyma, major intracranial vascular structures, white matter, and remaining bones were normal. Based on the imaging findings, the lesion was presumed to be composed of chondroid-type matrix arising from bone, most likely chondrosarcoma.

At a follow-up appointment 3 weeks later, the patient described complete resolution of diplopia despite receiving no treatment. Because of concern for malignant potential, the patient underwent tumor resection through an endoscopic transnasal approach. Pathology confirmed a Grade 2 chondrosarcoma (Fig. 2). Three months later, she remained free of diplopia. Extraocular movements were normal, and no other neurological deficits were present.

DISCUSSION

Neoplasm is a frequent cause of sixth nerve palsy. In a study of 46 patients with skull base tumors done by Pallini et al (20), all patients presented with this cranial nerve palsy. Similarly, Volpe et al (19) found 24/50 patients (49%) with skull base chordoma or chondrosarcoma presented with ocular symptoms as the initial manifestation. Sixth nerve palsy was most common, affecting 22 patients (46%) with chordomas and 23 (47%) with chondrosarcomas.

Chondrosarcomas occurring at the skull base account for only 6% of skull base tumors, with 0.15% of all intracranial chondrosarcomas (21,22). The most common sites occur at synchondroses, specifically the sphenoid–occipital and sphenoid–petrosal junctions (22). Involvement of the sixth nerve may be due to stretch or compression (22–24). The sixth nerve is particularly vulnerable to stretch in its portion from the pontomedullary junction to the dural entry point of the cavernous sinus and subject to compression within the cavernous sinus where it lies in close proximity to the internal carotid artery.

Chondrosarcomas are characterized by a slow growth pattern with a soft consistency and potentially can stretch and/or compress the sixth nerve to varying degrees (22). Balcer et al (5) reported a patient with Maffucci syndrome with intermittent diplopia. Volpe and Lessel (25) described 7 patients with skull base lesions (meningioma, chordoma, chondrosarcoma) who experienced improvement in their sixth nerve palsies to varying degrees. This variable clinical course with periods of spontaneous improvement in patients with parasellar lesions was noted by Thomas and Yoss (26) over 4 decades ago. Intermittent diplopia has been attributed to a variety of mechanisms including remyelination, axonal regeneration, transient compression with restoration of impaired blood flow, slippage of a nerve previously stretched by a tumor, or immune responses to the tumor (25).

In summary, Maffucci syndrome should be considered when cranial nerve palsies develop in the presence of unusual bone changes and subcutaneous hemangiomas (1,5,10,11,23). Sixth nerve palsy has been documented as one of the most frequent initial findings of an intracranial

![FIG. 1. Magnetic resonance imaging. Coronal magnetization prepared rapid gradient echo (MPRAGE) images, before (A) and after (B) intravenous contrast show heterogeneous enhancement of a left parasellar lesion (arrow). C. Axial T2 image also demonstrates heterogenous hyperintensity of the lesion.](image)
 lesion including chondrosarcomas in patients with Maffucci syndrome. Given the soft consistency of a chondrosarcoma and its growth pattern, intermittent or even resolving symptoms should not falsely reassure the clinician that the patient is following a benign clinical course.

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Optic Neuropathy Secondary to Eosinophilic Angiocentric Fibrosis

Adam P. Lloyd, MSc (Hons), MBChB, James D. Benimra, MBBS, FRCOphth, Adrian T. Warfield, MBChB, FRCPath, Balaji T. S. Prasad, MS, DNB, FRCS, Timothy D. Matthews, BSc, MBBS, DO, FRCS, FRCS, Shahzada K. Ahmed, BSc (Hons) DLO, MBChB, FRCS (ORL-HNS), PhD

Abstract: Eosinophilic angiocentric fibrosis (EAF) is a rare fibroinflammatory disorder with a predilection for upper respiratory tract submucosa. We report a 45-year-old man with progressive unilateral visual loss secondary to a retroorbital soft tissue mass with histological features consistent with EAF. The patient experienced marked improvement in vision after endoscopic optic nerve decompression through sphenoidomaxectomy.

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A 45-year-old man was referred for progressive visual loss in his left eye. Three years previously, he developed epistaxis and headaches and was found to have a positive antineutrophil cytoplasmic antibody and elevated protein 3 (PR3). His renal function was normal, and although a tissue diagnosis was not obtained, the patient was diagnosed with presumed granulomatosis with polyangiitis (GPA) (formerly Wegener granulomatosis). His symptoms resolved with steroid therapy, and he was maintained on steroids, azathioprine, and co-trimoxazole.

Twelve months before referral to our hospital, he became aware of a gradual reduction in vision in his left eye accompanied by mild retroorbital pain. On presentation to his local ophthalmology department, vision was 20/25 bilaterally, and choroidal folds were noted in the left eye. Inflammatory markers and PR3 were within normal limits. On neuroimaging, there was enhancing soft tissue at the left orbital apex, encompassing the intracranial optic nerve and involving the left cavernous sinus (Fig. 1). The bony anatomy showed evidence of sclerosis and thickening of the lateral wall of the opacified left sphenoid sinus. The patient was prescribed 80 mg of prednisone, but, on tapering, the vision...
in the left eye continued to deteriorate over the next 4 months to 20/100.

On referral to our institution, visual acuity was 20/15 in the right eye and 20/100 in the left eye. Color vision was reduced in the left eye, and there was a left relative afferent pupillary defect and a centrocecal scotoma in the left visual field. External ocular examination and ocular motility were normal. Although the right fundus appeared normal, there was left temporal disc pallor and choroidal folds.

The patient underwent endoscopic decompression of the left optic nerve through sphenoethmoidectomy. Biopsy specimens showed marked fibrosis with a perivascular onion-skin pattern and a lymphoplasmacytic infiltrate along with some eosinophils (Fig. 2). No granulomatous inflammation, necrotizing vasculitis, or obliterative thrombo philebitis were found. IgG4-positive cells were identified at a low ratio to IgG-positive cells, and serum IgG4 was normal. Fungal stains were negative. Histopathological features were consistent with a diagnosis of eosinophilic angiocentric fibrosis (EAF). The patient’s visual acuity improved to 20/30 two weeks after surgery.

EAF is a progressive fibroinflammatory disorder of upper respiratory tract submucosa of uncertain etiology. Since its original description as a variant of granuloma faciale in 1983 (1) and subsequent histological classification 2 years later (2), approximately 50 reported cases have been published (3). The pathognomonic histological features of EAF progress from an early submucosal vasculitis with predominant eosinophilic infiltrate to late stage whorled fibrosis of the microvasculature giving a characteristic “onion-skin” appearance (2,4).

Typically, EAF has a predilection for the nasal cavity with patients presenting with nonspecific symptoms such as nasal obstruction or epistaxis because of an enlarging sinonasal soft tissue mass (5). Ophthalmic manifestations have been reported infrequently, often with orbital involvement causing epiphora, proptosis, and diplopia (3,6–8). Our patient with EAF had a unique presentation with visual loss from compression of the retroorbital optic nerve. The pathophysiology of EAF remains uncertain. Some have suggested an association with allergic and atopic disorders (4), whereas there is recent evidence that EAF may be an IgG4 related systemic disease (9). EAF has been reported in association with granuloma faciale and atopy but has only once been documented in a patient with a confirmed diagnosis of GPA (10). It has been proposed that EAF may represent an exaggerated fibrotic reaction pattern rather than a distinct disease entity. Onion-skin fibrosis also has been reported in a sclerosing form of GPA of the orbit (11), in association with other expected features including necrotizing vasculitis and granulomatous inflammation. It is the absence of necrotizing vasculitis or granulomatous inflammation that distinguishes EAF histologically from other lesions with prominent eosinophilic infiltrates or onion-skin fibrosis (5,12).

FIG. 2. Eosinophilic angiocentric fibrosis. A. There is paucicellular dense fibro-hyaline tissue with fields of concentrically lamellated pattern (“onion skin”) consistent with an angiocentric distribution (hematoxylin & eosin, ×4). B. “Onion-skin” fibrosis is seen mantling small blood vessels and vascular remnants (hematoxylin & eosin, ×10). C. Moderately cellular fibromyxoid connective tissue is present with numerous eosinophil polymorphs, scattered small lymphocytes and a few mature plasma cells (hematoxylin & eosin, ×40). D. A mixed inflammatory cell population includes scattered mature plasma cells, a proportion of which show avid cytoplasmic IgG4 immunopositivity. There is some background reactivity, possibly representing serum IgG4 (IgG4 immunoperoxidase stain, ×40).
The management of EAF is challenging. Response has been poor to a variety of agents including azathioprine, dapsone, hydroxychloroquine, and tamoxifen (12). Surgical resection or debulking is commonly required with a high recurrence rate (5).

REFERENCES

Staphylococcus aureus Infection of the Optic Nerve

Senad Osmanovic, MD, Omar M. Al-Heeti, MD, Amy Y. Lin, MD, Sean P. Zivin, MD, Julie Ann Justo, PharmD, Stockton M. Mayer, DO, Vinay K. Aakalu, MD, MPH, Heather E. Moss, MD, PhD, Mahesh C. Patel, MD

Abstract: A 71-year-old woman presented with painful vision loss in the right eye followed by ophthalmoplegia. Magnetic resonance imaging demonstrated optic nerve sheath enlargement and enhancement. Biopsy of the optic nerve sheath revealed purulent and necrotic material that was positive for methicillin-sensitive Staphylococcus aureus. The patient underwent enucleation of the right eye and was treated with systemic antibiotics with clinical stabilization.

Imaging, pathological and treatment aspects of optic nerve sheath abscess are discussed.

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A 71-year-old woman reported headache and acute vision loss in her right eye. She had a history of diabetes mellitus with proliferative retinopathy and had uncomplicated nasal septoplasty 1 month before presentation. Review of systems was positive for myalgias, jaw tenderness, and weight loss. Visual acuity was reported to be count fingers in the right eye, with a right relative afferent pupillary defect and funduscopic changes of diabetic retinopathy. Erythrocyte sedimentation rate was 74 mm/h. There was concern for giant cell arteritis (GCA) as the cause of acute retrobulbar optic neuropathy, and she was treated with intravenous corticosteroids while temporal artery biopsy was arranged. When this failed to show evidence of arteritis, oral corticosteroids were gradually discontinued.
Nine days later, while on a steroid taper, the patient’s condition worsened with further decline of vision in right eye, new right eye ophthalmoplegia, and onset of fever and chills. Temperature was 37.9°C. Neuro-ophthalmologic examination revealed visual acuity of no light perception in the right eye and 20/40 in the left eye. The right pupil was fixed at 2 mm and did not react directly or consensually. Ductions of the right eye were limited to only slight incyclotorsion on attempted downgaze. There was 2 mm of right proptosis and complete right ptosis. Intraocular pressures were normal and symmetric. There was mild injection of the right conjunctiva, and the anterior chamber appeared quiet. Ophthalmoscopic examination revealed right optic disc edema with extension of subretinal fluid into the macula and occlusion of the central retinal artery and vein. Left eye and neurological examinations were normal.

Peripheral white blood cell count was elevated at 12,300 cells per microliter with 76% neutrophils. Cerebrospinal fluid had 480 white blood cells per microliter (43% neutrophils, 48% lymphocytes), protein of 80 μg/dL (normal, 15–45 μg/dL), and negative cultures. Ultrasonography demonstrated a heterogeneous subretinal mass communicating with the optic nerve. Magnetic resonance imaging (MRI) showed diffuse enhancement and enlargement of the optic nerve sheath as well as restricted diffusion (Fig. 1). The right cavernous sinus and paranasal sinuses appeared normal. Endoscopy did not reveal paranasal sinus infection.

The patient was empirically started on intravenous vancomycin, cefepime, acyclovir, and voriconazole for a suspected intraocular infection of unknown etiology. Echocardiogram, blood cultures, viral studies, and the remainder of an infectious source workup were negative. Because of worsening of her clinical condition, an anterior orbitotomy was performed. Purulent material was expressed on incision of the optic nerve sheath. Grain stain showed gram-positive cocci.

Over the next 24 hours, the patient developed temporal field loss in the left eye and MRI demonstrated new involvement of the optic chiasm (Fig. 2).

A decision was made to enucleate the right eye, and at the time of surgery, the orbit was irrigated with vancomycin and gentamicin. Pathology showed a neutrophilic infiltrate with cell debris in the optic nerve, peripapillary retina, vitreous, choroid, and subarachnoid space (hematoxylin & eosin). Inset shows the infiltrate composed of neutrophils and necrotic debris, consistent with an abscess. B. Choroidal abscess is present (hematoxylin & eosin). Inset reveals the abscess contains neutrophils and debris surrounded by plasma cells.
genitourinary), are features that may heighten suspicion for possible non-GCA diagnoses.

*Staphylococcus aureus* is an aerobic bacterium that is found in 20%–80% of the general population, primarily in the nares (1). *Staphylococcus aureus* infections are fairly ubiquitous, and disseminated infections can result in significant morbidity and mortality (2). Controversy still remains over which isolate, MSSA, or methicillin-resistant *S. aureus*, is more virulent (3–5). The virulent nature of MSSA was well demonstrated in our patient, as she had rapid spread of infection from the optic nerve to the optic chiasm despite appropriate antimicrobial therapy. Successful treatment was achieved with aggressive use of antibiotics (6,7) and surgical intervention.

In a retrospective study of 163 patients with brain abscesses, *S. aureus* was the causative agent in 21% (8). An unidentified source of the abscess was common, occurring in 19% of patients. Similarly, a predisposing factor for orbital infections is often not identified (9). We hypothesize that our patient’s infection may have been due to transient bacteremia at the time of her nasal septoplasty. This led to seeding of her optic nerve and subsequent abscess formation supported by findings on diffusion-weighted imaging (10). Immunosuppression due to her diabetes likely was a contributing factor. Use of corticosteroids before antibiotic treatment may have further compromised her immunological response.

**REFERENCES**

Neuro-Behçet Disease Presenting With Oculopalatal Tremor

Michael L. Morgan, MD, PhD, Angelina Espino Barros Palau, MD, Andrew G. Lee, MD, Rod Foroozan, MD

Abstract: A 39-year-old woman with a history of Behçet disease presented for evaluation of oscillopsia that began postpartum. Examination showed oculopalatal tremor (OPT), documented videographically. Brain magnetic resonance imaging revealed bilateral pseudohypertrophy of the inferior olivary nuclei. Treatment with gabapentin was initiated for OPT presumed secondary to neuro-Behçet disease.

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Behçet disease (BD) is an autoimmune disorder geographically associated with the Silk Road and featuring recurrent oral and genital ulcers and uveitis as well as potential involvement of multiple organ systems, including the central nervous system (1). As with many autoimmune diseases, pregnancy provides some protection with potentially increased relapse risk in the postpartum period (2). Involvement of the central nervous system is termed neuro-Behçet disease (NBD), with the brainstem most frequently affected.

Palatal tremor (PT), also termed palatal myoclonus, refers to rhythmic jerking movements of the throat and soft palate associated with damage to the dento-rubro-olivary pathways, referred to as the triangle of Guillain and Mollaret (3). Several cases of PT have been associated with NBD (4–7). When pendular ocular oscillations synchronous with PT are also present, the syndrome is referred to as oculopalatal tremor (OPT) or oculopalatal myoclonus (8). Our patient with BD developed OPT in the postpartum period.

Case Report

A 39-year-old woman with a history of BD, Hashimoto thyroiditis, and hypertension was referred for evaluation of nystagmus. She was diagnosed with BD 16 years prior after biopsy of recurrent genital ulcers. She also had developed oral ulcers and uveitis in the past and had been treated with etanercept and methotrexate in the early years after diagnosis. She also had been treated intermittently with dapsone, which was discontinued several times after development of methemoglobinemia and corticosteroids 3 months before our evaluation and azathioprine more recently.

Her family history was remarkable for rheumatoid arthritis and hypothyroidism. She drank alcohol moderately and was a former tobacco smoker.

Six weeks after delivering a healthy baby, the patient noted poor balance on attempted resumption of physical exercise and soon thereafter rotary oscillopsia involving the right eye. Two months later, she developed a throbbing sensation in her throat and observed her uvula jerking rhythmically. These symptoms continued uninterrupted. Magnetic resonance imaging (MRI) of the brain revealed pseudohypertrophy of the inferior olivary nuclei bilaterally. Her neurologist detected nystagmus corresponding to her oscillopsia. A vestibular evaluation was consistent with right vestibular dysfunction and benign paroxysmal positional vertigo. Multiple Epley maneuvers provided no improvement.
Nine months before our evaluation, neurological examination was remarkable for flattening of the left nasolabial fold, PT, proximal weakness (4/5 strength) in the upper extremities and in the right lower extremity, bilateral patellar hyperreflexia, and unsteady gait. Cerebrospinal fluid analysis was unremarkable. Twenty-two months after onset of symptoms, brain MRI showed T2 hyperintensity bilaterally in the ventral medulla with faint contrast enhancement (Fig. 1).

Neuro-ophthalmic examination demonstrated rotary pendular oscillations of both eyes, greater on the right (see Supplemental Digital Content, Video, http://links.lww.com/WNO/A108). Additionally, she had rhythmic movements of the angles of her mouth, uvula, and palate, and her speech was dysarthric. The rotary pendular ocular oscillations and palatal movements were synchronous with a frequency of approximately 1–2 Hz. The remainder of her ophthalmologic examination was normal.

Given her clinical and MRI findings, she was diagnosed with OPT and prescribed gabapentin 300 mg 3 times daily. Her symptoms and examination remained unchanged 2 months later, and consideration was being given for treatment with memantine or increased immunosuppression.

**DISCUSSION**

OPT arises from disruption of the dento-rubro-olivary pathways (8). Brainstem ischemia and hemorrhage account for 60%–70% of cases with additional causes including trauma, infection, inflammation, demyelination, and possibly toxicity from metronidazole, lithium, carbamazepine, and ciprofloxacin. Pseudohypertrophy of one or both inferior olivary nuclei (ION) is the neuroimaging hallmark of OPT. Our patient had bilateral OPT and bilateral ION pseudohypertrophy. In a review of the literature, Pearce (3) reported that in 287 cases of PT, no cause could be found in 25% and these patients typically lacked radiographic abnormalities. The finding of bilateral ION pseudohypertrophy without other radiographic abnormalities in our patient is unusual. However, her first MRI was performed over a year after symptoms began, and a brainstem or cerebellar abnormality might have been present transiently.

Our patient experienced gait imbalance 6 weeks after delivery. We presume that she developed NBD at that time with bilateral damage to the dento-rubro-olivary pathways. OPT symptoms began approximately 2 months postpartum. As with many autoimmune diseases, BD often improves during pregnancy with relapses sometimes occurring in the postpartum period. In 27 BD exacerbations across 84 pregnancies in 50 patients, 19 occurred during 9 months of pregnancy (0.025/mo) compared with 18 in 3 months postpartum (0.071/mo) (2).

The occurrence of PT due to NBD has been documented in case reports (4–7). However, OPT occurring in patients with NBD is rare. In a series of 4 cases with PT, 1 patient had NBD (9). In that patient, the tremor was more extensive, affecting the palate, throat, and diaphragm with subsequent involvement of the face, eyes, neck, and shoulder girdles.

**FIG. 1.** Pseudohypertrophy of the bilateral inferior olivary nuclei (ION). A, Fluid-attenuated inversion recovery magnetic resonance imaging shows hyperintensity and enlargement of the bilateral ION (arrows). B, T1 imaging also demonstrates enlargement. **C,** The ION faintly enhanced with gadolinium contrast (arrowheads).
STATEMENT OF AUTHORSHIP

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Unilateral Internuclear Ophthalmoplegia as an Isolated Presentation of Metastatic Melanoma

Sunil Kumar, MS, FRCS, Shefalee S. Kent, MD, FRCSC, Arun N. Sundaram, MD, MSc, FRCP, Manas Sharma, MD

Abstract: Multiple sclerosis in younger patients and brainstem infarction in the elderly are the most common causes of internuclear ophthalmoplegia (INO). We report unilateral INO as the isolated clinical manifestation of a large, solitary, metastatic melanoma in the pons. Brain metastasis can present as INO.

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Brainstem tumors can cause various gaze disorders (1,2). Melanoma is the second most common cause of brain metastasis after carcinoma of lung (3) and has a highly characteristic signal pattern on magnetic resonance imaging (MRI). We report INO as the presenting manifestation of solitary metastatic melanoma. The metastasis was remarkable in its large size and the absence of other neurologic findings.

CASE REPORT

A 52-year-old man was admitted to hospital with a complaint of horizontal diplopia for 1 day. His medical history was remarkable for Crohn disease, amyloidosis, and intestinal melanoma. He had undergone bowel resection on 3 occasions for Crohn disease. Amyloidosis caused renal failure leading to a renal transplant 10 years earlier. Intestinal melanoma was detected 1 year before admission, and he received chemotherapy for 5 months. He developed metastases in the pelvis and both femurs and was treated with radiotherapy.

Neuroophthalmic examination revealed visual acuity of 20/30, right eye and 20/25, left eye. Color vision testing, pupillary reactions, visual fields, and fundi were normal. The patient was unable to adduct the left eye using saccades, pursuit, or vestibular–ocular reflex motion, but he was able to converge. Ductions were full in right eye. Abducting jerk nystagmus of the right eye was present in right gaze. Saccades were normal in the right eye but rightward saccades in the left eye from abduction to the midposition were slow. Vertical eye movements were intact, and there was no vertical ocular misalignment. The remainder of the neurological examination was normal.

Brain MRI demonstrated a solitary 1.7 cm contrast-enhancing mass localized within the pons with partial effacement of fourth ventricle (Fig. 1). Results of susceptibility-weighted imaging were consistent with the presence of blood products within the tumor (Fig. 2). These MRI findings were characteristic of metastatic melanoma. Multiple focal abnormalities were also noted in the cranial vault consistent with metastatic disease.

The pontine metastasis was treated with gamma knife radiosurgery followed by whole brain radiation and chemotherapy with fotemustine. Four months later, there was marked improvement in the pontine metastasis (Fig. 3). At 5- and 9-month follow-up examinations, the range of adduction of left eye was full and jerk nystagmus of the abducting right eye had resolved. Slow saccades of the abducting left eye were the only residual finding of the previously complete INO.

DISCUSSION

Approximately 5% of reported cases of INO are due to neoplastic cause (2,4), which include medulloblastoma (5), glioma (6), cavernoma (7), astrocytoma (5), dermoid and...
epidermoid tumor (8), carcinomatous meningitis (9), and paraneoplastic syndrome (10).

Metastases may be the first clinical evidence of the neoplasm in patients with central nervous system metastatic disease (11), and brainstem involvement may occur (12,13) rarely presenting as INO (14). In a retrospective analysis, brain metastases have been reported to cause INO or the one-and-a-half syndrome in fewer than 1% of cases (2).

This may be due to the fact that the posterior circulation accounts for <25% of total cerebral blood flow. Therefore, hematogenous spread of brain metastasis is less likely to involve the brainstem.

Approximately 37% of patients with melanoma eventually develop brain metastasis and, in autopsy reports, 75% of those who died of melanoma developed brain metastasis (15). The imaging features of metastatic melanoma are distinctive because of the presence of melanin and the propensity for hemorrhage. Both hemorrhage and melanin can produce hyperintense appearance on T1-weighted imaging (Fig. 1) while showing signal intensity loss (susceptibility artifact) on susceptibility-weighted imaging (Fig. 2) (16).

Our patient illustrates that isolated INO can be the initial presentation of melanoma metastatic to the brain and

![FIG. 1. A. T1 sagittal magnetic resonance (MRI) imaging shows large solitary mass with peripheral hyperintensity within the pons. After contrast administration, sagittal (B) and axial (C) MRIs demonstrate avid enhancement of the pontine mass.](image1)

![FIG. 2. Susceptibility-weighted axial image reveals dark rim at the margins of the lesion with a nodular appearance on the posterior aspect, signifying presence of blood products.](image2)

![FIG. 3. T1 sagittal magnetic resonance imaging reveals resolution of the mass 4 months after gamma knife radiosurgery.](image3)
that the extent of metastasis may not be evident from the limited neurological deficits detected clinically.

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**STATEMENT OF AUTHORSHIP**

Category 1: a. Conception and design: S. Kumar; b. Acquisition of data: S. Kumar and M. Sharma. Category 2: a. Drafting the manuscript: S. Kumar and M. Sharma; b. Revising it for intellectual content: S. Shukla and A. N. Sundaram. Category 3: Final approval of the completed manuscript: S. Kumar.

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Fourth and Sixth Nerve Palsies Due to Herpes Simplex 1 Infection

Evangelos Anagnostou, MD, Vasiliki Mouka, MD, Elisabet Kemanetzoglou, MD, Evangelia Kararizou, MD

Abstract: Ocular motor cranial nerve palsies of viral etiology are uncommon and, when accompanied by skin lesions, zoster ophthalmicus is the most frequent diagnosis. We describe the case of a 68-year-old woman who developed fourth and sixth nerve palsies 3 days after appearance of a painful vesicular skin rash on the left side of her forehead. Neuroimaging was normal but polymerase chain reaction (PCR) testing of the cerebrospinal fluid was positive for Herpes Simplex 1 and negative for Varicella Zoster. The patient was treated with intravenous acyclovir, and the cranial nerve palsies resolved over 7 weeks. Although the similarity of the cutaneous vesicular eruption in our patient to that seen with zoster might have led to an incorrect diagnosis, acyclovir seems to be safe and effective for both viral etiologies.

CASE REPORT

A 68-year-old woman developed an itchy vesicular rash on her left forehead 5 days before admission. She was prescribed topical acyclovir cream, and 3 days later, she complained of horizontal and vertical diplopia. On admission, she had intermittent stabbing headache in the left periorbital area and an erythematous skin rash with 2 clearly discernible vesicles in the dermatomal distribution of the first division of the left trigeminal nerve. Visual acuity, pupillary reactions, slit lamp examination, and ophthalmoscopy were normal. The patient had a marked right head tilt. In primary position, there was a left esotropia of 20 prism diopters and a left hypertropia of 10 prism diopters. There was limited abduction of the right eye, and the remainder of the neurological examination was normal.

Magnetic resonance imaging of the brain and orbits was unremarkable. Lumbar puncture revealed 3 lymphocytes per cubic millimeter, protein of 35 mg/dL (normal: 15–45 mg/dL), and glucose of 70 mg/dL. CSF samples were sent for polymerase chain reaction (PCR) testing for Herpes viruses, and the patient was started on intravenous (IV) acyclovir 10 mg/kg 3 times daily with the preliminary diagnosis of herpes zoster ophthalmicus.

Over the next 5 days, the vesicular rash began to resolve. PCR testing was positive for HSV1 DNA and negative for the other herpes viridae (Herpes Zoster, HSV2, Epstein–Barr, and Cytomegalovirus). Repeat PCR testing of the same CSF sample revealed the same results. Twelve days after symptom onset and while the patient was still on intravenous acyclovir, hematologic testing showed elevated immunoglobulin G (IgG) levels for both HSV1 and HVZ but was negative for IgM antibodies. At that time, the skin lesions were restricted to a small area on the left forehead (Fig. 1), and the head tilt had improved. Eye

Althought a number of viridae families have been labeled as neurotropic and are able to cause meningitis or encephalitis, only a few have been documented to cause cranial nerve infections. These include human immunodeficiency virus type 1, Cytomegalovirus, Epstein–Barr Virus, herpes simplex virus (HSV) 1 and 2. The Herpes Zoster virus (VZV), Hepatitis C and Hepatitis B virus, human T-cell lymphotropic virus type 1, and West Nile virus (1). Viral causes constitute a rare subgroup of painful ophthalmoplegia cases (2). Although VZV is a well-described pathogen leading to third, fourth, and sixth nerve palsies, only single case report exists for other viruses (3–7). We are unaware of Herpes simplex virus type 1 (HSV1) being associated with a fourth or sixth nerve palsy.

Department of Neurology, Eginition Hospital, University of Athens, Athens, Greece.

The authors report no conflicts of interest.

Address correspondence to Evangelos Anagnostou, MD, Department of Neurology, Eginition Hospital, University of Athens, Vas Sophias Avenue, 74, Athens 11528, Greece; E-mail: granavan@yahoo.com

movement recordings revealed normal amplitude for the left eye on horizontal leftward saccades but markedly reduced angular velocity (Fig. 2), consistent with left sixth nerve paresis. On discharge from the hospital, the patient completed 14 days of IV acyclovir and reported no residual horizontal or vertical double vision. Head tilt also resolved, and the patient denied any facial pain or dysesthesias. Examination 7 weeks later showed complete recovery of both ocular motor cranial nerve palsies.

**DISCUSSION**

Our patient developed ipsilateral fourth and sixth nerve palsies after a short period of periorbital and temporal pain accompanied by a herpetic rash. PCR conducted on a cerebrospinal fluid obtained 3 days after onset of diplopia was positive for HSV1 DNA. Treatment with intravenous acyclovir was initiated and the ocular motor cranial nerve palsies resolved over 7 weeks.

Neuropathy of the third, fourth, or sixth nerves due to HSV is rare. There is one report of 2 patients with third nerve palsies with pupillary involvement caused by HSV1 (5). The diagnosis was made by HSV1 antibodies in the CSF detected by ELISA. A fourth nerve palsy has been reported in a patient recovering from HSV1 encephalitis (8). The extent of the lesions near the Sylvian aqueduct and fourth ventricle of this case report also might have caused a skew deviation. The authors do not provide a detailed description of the ocular motor examination.

HSV1 has been linked to nonocular motor cranial neuropathies. It has been implicated in the pathogenesis of “idiopathic” peripheral facial nerve palsy (Bell palsy). HSV1 DNA has been detected in endoneural fluids of the facial nerve or the auricular muscle in 9 of 14 patients with idiopathic facial palsy (9). Vestibular neuritis also has been causally linked to a HSV1 infection, although here data are more sparse (10).

Despite the rareness of clinical eye movement abnormalities in HSV1 infections, the presence of HSV1 DNA has been demonstrated in human ocular motor nuclei. Theil et al (11) examined histological sections of 5 human brainstems by means of DNA amplification of oculomotor, trochlear, and abducens nuclei. HSV1 was found in all nuclei.

How does a viral pathogen for cutaneous infections such as HSV1 cause a cranial neuropathy? It is believed that after primary infection, the virus gains access to axon endings within the mucocutaneous surface and is transported to the trigeminal ganglion. The viral genome is maintained within the ganglion, which serves as a reservoir for viral nucleic acids. Latent herpetic infection is a lifelong state. Under...
certain circumstances, the virus can reactivate and travel to regions innervated by the fifth nerve causing recurrent disease. It remains unclear how the virus travels from the sensory ganglia and sensory axons to motor fibers. In a case of ophthalmoplegia due to herpes zoster, Lavin et al (12) demonstrated with histopathology that inflammation of the ocular motor cranial nerves was located within the cavernous sinus, where they are in close proximity to sensory nerves.

In our patient, PCR testing of CSF established HSV1 as the cause of the ocular motor cranial neuropathies. PCR has become the gold standard for the diagnosis of HSV1 infections even in the absence of serum IgM antibodies. In part, this is because the rise of IgM antibodies occurs in a narrow time window and shows a lower sensitivity than PCR (13–15). Serum examination in our patient was performed 12 days after symptom onset, beyond the optimal detection period for IgM antibodies.

REFERENCES

Isolated Left Homonymous Hemianopia Secondary to a Pericatheter Cyst—A Rare Presentation of a Ventriculoperitoneal Shunt Failure


Abstract: A 26-year-old woman developed a left homonymous hemianopia 1 week after placement of a ventriculoperitoneal shunt through a right parieto-occipital approach. Computed tomography demonstrated a parenchymal cyst in the right occipital lobe. After shunt revision, there was concomitant resolution of the cyst and visual field defect over 1 month. The literature is reviewed regarding this unusual complication of ventriculoperitoneal shunt failure.

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Hydrocephalus is a common problem after subarachnoid hemorrhage (SAH) often requiring permanent cerebrospinal fluid (CSF) diversion (1). Obstruction is the most common cause of shunt failure with the most common site located intracranially (2). Signs and symptoms of increased intracranial pressure after shunt failure include headache, nausea, vomiting, and ataxia. Neuro-ophthalmic findings included diplopia, upward gaze palsy, and papilledema. We report a patient who developed a reversible homonymous hemianopia as a rare complication of shunt failure.

CASE REPORT

A 26-year-old woman had an SAH secondary to a ruptured posterior communicating artery aneurysm. Computed tomography (CT) of the head showed dense SAH with intraventricular hemorrhage (IVH) and Hunt/Hess score 3 at the time of admission. The patient underwent clipping of the aneurysm with placement of an external ventricular drain (EVD). Postoperatively, she was oriented and followed commands and consistently drained high volumes of CSF. Once the IVH had cleared, the patient was weaned off EVD. However, she complained of persistent and worsening headache, which improved when the EVD was opened. Twenty-one days after SAH, the patient underwent an uncomplicated right parieto-occipital ventriculoperitoneal shunt with the peritoneal catheter placed under direct visualization and a Strata valve set at 1.0. Before discharge to a rehabilitation facility, physical examination revealed the patient to be neurologically intact, and CT showed the ventricular catheter in satisfactory position (Fig. 1).

One week later, the patient returned for routine follow-up and reported a new visual disturbance for less than 1 day. She denied nausea, ataxia, or headache and was afibrile with a supple neck. Pupils were equal and reactive to light, and extraocular movements were full. Visual field testing revealed a left homonymous hemianopia (Fig. 2), and ophthalmoscopy was normal. The remainder of the neurologic examination was unremarkable.

Brain CT demonstrated a new cystic area surrounding the right ventricular catheter measuring 38 × 51 mm (Fig. 3). There was no significant ventriculomegaly or transpendymal flow and brain magnetic resonance imaging did not show evidence of infarction. An abdominal radiograph revealed the distal shunt catheter coiled in the right upper quadrant (Fig. 4). The patient underwent revision of the distal catheter, and 40–50 mL of CSF under high pressure were drained once the abdominal incision was opened. The shunt catheter was found to be coiled in the subcutaneous space. The peritoneal cavity was explored to ensure that there were no adhesions or pseudocyst, and the catheter was repositioned in the peritoneal space.
On postoperative day 3, the patient was discharged reporting improvement in the visual deficit. Testing 1 week later showed full visual fields. On CT, the cystic area was reduced in size to $27 \times 16$ mm and resolved 1 month later (Fig. 5).

**DISCUSSION**

CSF edema and cyst formation after shunt operations has been reported periodically (Table 1). Using the PubMed database, a literature search was conducted using a combination of the key words hydrocephalus, homonymous hemianopia, shunt malfunction, visual deficits, shunt failure, CSF edema, porencephalic cyst, pericatheter cyst, and intraparenchymal cyst. This yielded 13 articles that included cases dealing with cysts or CSF edema after shunt complications from 23 patients. Three articles in Japanese and 1 in French were excluded. All patients had improvement in CSF edema or cysts and their symptoms after shunt revision with the exception of the third case reported by Sugimoto et al (9). That patient required placement of a cyst peritoneal shunt in addition to ventriculoperitoneal shunt revision. The youngest patient included in this search was 32 days (6), and the oldest patient was 65 years (4). The interval between the time that the shunt was
placed and the time the patient began experiencing complications ranged from 10 days (10, 11) to 12 years (7). Most patients required shunt revision although shunt removal and observation were also reported.

Most patients with VP shunt failure with CSF edema or cyst formation present with headache, vomiting, seizures, or drowsiness (3,7–11,13,14). Less typical presentations include isolated hemiparesis (4), speech and writing disturbances (5), or visual abnormalities. Chiba et al (11) reported a 58-year-old man who developed a low-density area on CT in the right parietal white matter and a left homonymous hemianopia. At surgery, an “excessive amount” of CSF was found under the dura, and with drainage and shunt revision, the visual field defect resolved. Kojima et al (15) documented a similar course in a patient with a left homonymous hemianopia that resolved with revision of a VP shunt. The authors proposed peritubular CSF edema in the right occipital area as the cause of the visual field defect.

We believe that, in our patient, distal shunt failure due to periperitoneal migration of the catheter resulted in elevated intracranial presence. Fluid tracked along the path of least resistance around the shunt catheter in the occipital lobe. Ventriculomegaly did not occur because the ventricles were noncompliant after SAH and were unable to expand to accommodate the increased CSF volume. The homonymous hemianopia was consistent with the location of the fluid accumulation in the right occipital lobe.
<table>
<thead>
<tr>
<th>Author</th>
<th>No. of Cases</th>
<th>Age</th>
<th>Interval Between Shunt Placement and Complications</th>
<th>Primary Diagnosis</th>
<th>Presenting Symptoms</th>
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<tr>
<td>Iqbal et al, (3)</td>
<td>2</td>
<td>10 y</td>
<td>2 y</td>
<td>Lumbosacral meningomyelocele</td>
<td>Headaches, vomiting, increasing weakness, and spasms in the right arm</td>
<td>Distal</td>
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<td>Shekawat et al, 2012 (4)</td>
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<td>65 y</td>
<td>1 mo</td>
<td>Posttraumatic hydrocephalus</td>
<td>Headaches with nausea</td>
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<td>Vajramani and Fugleholm, 2005 (5)</td>
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<td>51 y</td>
<td>2 y</td>
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<td>Speech and writing disturbance</td>
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<td>Shunt revision</td>
</tr>
<tr>
<td>Rim et al, 2011 (6)</td>
<td>1</td>
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<td>2 mo</td>
<td>Hydrocephalus after germinal matrix-intraventricular hemorrhage</td>
<td>Head enlargement and tense fontanel</td>
<td>Proximal</td>
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<td>Owen and Pittman, 2003 (7)</td>
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<td>12 y</td>
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<td>Headache, vomiting, and lethargy</td>
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<td>Balasubramaniam et al, 2013 (8)</td>
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<td>1.5 y</td>
<td>1 y</td>
<td>Meningomyelocele</td>
<td>Seizures</td>
<td>Proximal</td>
<td>Shunt removal</td>
</tr>
<tr>
<td>Sugimoto et al, 1991 (9)</td>
<td>3</td>
<td>5 mo</td>
<td>2 mo</td>
<td>Hydrocephalus, meningocele, Chiara malformation</td>
<td>Vomiting</td>
<td>Unknown</td>
<td>Shunt revision and CP shunt added</td>
</tr>
<tr>
<td>Prasad et al, 1991 (10)</td>
<td>2</td>
<td>45 y</td>
<td>10 d</td>
<td>Hydrocephalus</td>
<td>Less alert</td>
<td>Distal</td>
<td>Shunt revision</td>
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<tr>
<td>Chiba et al, 1982 (11)</td>
<td>3</td>
<td>58 y</td>
<td>2 wk</td>
<td>CPA mass with hydrocephalus</td>
<td>Signs of increased ICP, headache, left homonymous hemianopia, hypesthesia, weakness</td>
<td>Distal</td>
<td>Shunt revision</td>
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<tr>
<td>Sinha et al, 2008 (12)</td>
<td>2</td>
<td>4 y</td>
<td>4 y</td>
<td>Meningomyelocele</td>
<td>Signs of increased ICP</td>
<td>Distal</td>
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<tr>
<td>Sakamoto et al, 1994 (13)</td>
<td>4</td>
<td>7 y</td>
<td>3 mo; 12 mo</td>
<td>Myelolomeningocele</td>
<td>Signs of increased ICP</td>
<td>Distal</td>
<td>Shunt revision</td>
</tr>
</tbody>
</table>
### REFERENCES


Treatment of Neuro-Ophthalmic Sarcoidosis

Larry P. Frohman, MD

Background: Because of the rarity of neuro-ophthalmic sarcoidosis, there are no therapeutic guidelines based on evidence-based medicine for this disorder.

Evidence Acquisition: Review of literature combined with personal experience.

Results: Corticosteroids are the preferred initial therapy for neuro-ophthalmic sarcoidosis. If patients cannot tolerate the requisite dose of corticosteroid needed to control their disease, or if corticosteroids fail to adequately control the disease process, the choices of a second agent are based on the consideration of rapidity of clinical response and the safety profile.

Conclusions: Although methotrexate and mycophenolate mofetil are the medications that are often selected after corticosteroid failure, more rapidly acting agents that have been used are infliximab and intravenous cyclophosphamide.

METHODS

Personal case records of sarcoid patients with neuro-ophthalmic manifestations is evaluated by the neuro-ophthalmology service of New Jersey Medical School from 1989 to 2012 were reviewed, combined with an OVID-MEDLINE search. The search covered 1945 to 2013. Each individual therapeutic agent was cross-referenced with the search terms “sarcoid” and “neurosarcoid.” Relevant papers were reviewed.

RESULTS

In 1985, Stern et al (5) reported treatment of 33 neurosarcoid patients. Optic neuropathy (ON) was infrequent in his series (1/33 patients). Improvement on prednisone alone was seen in 19/21 patients. Other reports supported the efficacy of corticosteroid treatment (6–10), including that by Beardsly et al (9) in which 6/11 (55%) of their patients with ON responded to steroids. Another series (10) documented the clinical course in 20 patients with neuro-ophthalmic sarcoid and 14 with ON. With steroid therapy, 5 showed improvement in vision, 5 remained stable, and 4 worsened. Six of the 14 patients subsequently received immunosuppressive treatment: 1 improved, 3 stabilized, and 2 worsened. In a series of 69 patients with neurosarcoid, Zajicek et al (11) included 26 with ON. Improved optic nerve function with corticosteroids varied, with relapse common as corticosteroids were tapered. The authors concluded that “Although this is the largest single series of patients with neurosarcoidosis yet reported, with visual loss, diplopia, or homonymous visual field defects. The frequency of neuro-ophthalmic disease is not known, but that of optic nerve involvement ranges from 1% to 5%.

The natural history of neuro-ophthalmic sarcoid is unknown. There is neither consensus on the need to treat all cases nor agreement on the optimal therapeutic approach (2,3). Asymptomatic cases of neuosarcoid might not require treatment (4). This is generally not a consideration for neuro-ophthalmic sarcoid.

The prevalence of sarcoidosis is 6–10/100,000 worldwide. In the United States, this figure varies by race: in whites, it is 5/100,000 and in African Americans it is 40/100,000. Ocular involvement occurs in the course of 22% of cases. Neurosarcoid refers to sarcoidosis involving the brain, cranial nerves, and spinal cord. Neuro-ophthalmic sarcoid is a subset of neurosarcoid that involves the afferent and efferent visual systems.

The facial nerve is the most commonly affected cranial nerve in sarcoidosis reported in 5%–16% of patients (1). Neuro-ophthalmic involvement most typically presents as...
It is unknown whether neuro-ophthalmic disease should be included in such therapeutic recommendation. Although corticosteroids are the preferred initial therapy for neuro-ophthalmic sarcoid, 1 large retrospective study highlighted the variability of response to medication (12). The records of 54 patients with neurosarcoi, 19 patients with optic nerve disease, and 3 with other neuro-ophthalmic signs (ptosis = 1 and diplopia = 2) were reviewed. Treatment data were provided in 53 patients, of whom 35 were begun on corticosteroids alone, 12 received no specific treatment, 5 received immunosuppressants without corticosteroids, and 1 received corticosteroids with an immunosuppressive agent. At the conclusion of the study, 6 patients were on corticosteroids and 15 required steroids with immunosuppressives. Many of the patients with ON had a poor visual outcome.

Therapeutic outcomes were assessed in a retrospective study of 47 patients with definite or probable neurosarcoi (13). Although 6 cases had ON, the specific outcomes in this subgroup were not reported. The study had an intentional treatment bias where those patients (n = 26) considered at high risk for neurologic progression were treated at the onset with corticosteroids and immunosuppressives. Those not felt to be at high risk received corticosteroids alone (n = 20) or no treatment (n = 2). Despite this treatment assignment bias, after a mean observation period of 44 months, of the group perceived to be at higher risk, 18/26 had improvement, 4/26 remained stable, and 4/26 worsened. Of those with milder disease receiving steroids alone, only 7/20 patients improved, 11/20 remained stable, and 2/10 worsened.

It has become clear that treatment of sarcoi ON is a continuum, ranging from a case of ON with spontaneous recovery (14) to patients who may progress to blindness despite aggressive therapy.

That cases without preexisting sarcoi and without classic fundus findings are now being diagnosed as sarcoi instead of labeled as idiopathic optic neuritis may contribute to the dichotomy of opinion on corticosteroid sensitivity of ON.

Although corticosteroids are first-line therapy, there is recognition that not all cases of neurosarcoi are controlled with corticosteroids, and the concept of initial multidrug therapy has been raised. Hoitsma et al (15) have noted that “Combination therapy of corticosteroids and alternative immunosuppressive agents immediately at the time of initial diagnosis are recommended in cases with poor prognosis such as intracranial masses and myelopathy.” It is unknown whether neuro-ophthalmic disease should be included in this therapeutic recommendation.

**ALTERNATE THERAPEUTIC AGENTS**

Choosing an alternate drug requires considering its safety and efficacy profile, and the lag time until clinical response might be expected (Table 1). In the neurosarcoi literature, a commonly used surrogate measure of efficacy is the mean reduction in corticosteroid dose achieved with the initiation of an additional therapeutic agent. One series reported that 26 patients with neurosarcoi in whom a variety of different medications including chlorambucil, cyclosporine, cyclophosphamide, azathioprine, and methotrexate as well as radiation therapy (RT) led to a decrease in prednisone dosage of 10–20 mg/d in only 38% of cases (81). In another series of patients with neurosarcoi, corticosteroids alone led to improvement in 14/48 (29%) patients, methotrexate in 17/28 (61%), and cyclophosphamide in 9/10 (90%) (21). In a study of 40 patients with neurosarcoi where corticosteroids alone proved beneficial in 40% of patients, several immunosuppressants were used in the remaining patients. Overall, only 13/40 (32.5%) had complete recovery (82). Of 54 patients with neurosarcoi (35% with ON), 6 (11%) required long-term maintenance on prednisone, 37 (69%) required an immunosuppressant with or without corticosteroids, and 11 (20%) required no maintenance therapy (12). In a report of 15 patients with neuro-ophthalmic sarcoi other than ON, 13/15 (87%) responded to oral corticosteroids and the other 2 required cyclosporine (1).

**Agents to Consider as Alternate Therapy**

Methotrexate was initially used in a patient with sarcoi who had failed the treatment with corticosteroids and vinblastine (16). Baughman et al (17) reported a randomized study of 15 patients with systemic (not neurologic) sarcoi prescribed prednisone with methotrexate vs prednisone and placebo. At 12 months, the group treated with methotrexate achieved a 50% reduction in the corticosteroid dose. In another study, 17/28 (61%) patients with neurosarcoi who failed the treatment with corticosteroids responded to methotrexate (84). It has been suggested that in neurosarcoi, one may need to use combination therapy with methotrexate at the onset (3). Methotrexate has been used in a series of 3 patients with ON intolerant of high-dose corticosteroids. All stabilized, or improved and required less corticosteroids (18). In 6 cases of sarcoi ON refractory to steroids, 4 (67%) had a good response to methotrexate (1 in conjunction with corticosteroids and thalidomide) and 2 (33%) were treatment failures (19). There is some consensus that in the treatment of neurosarcoi, methotrexate is the drug of choice when corticosteroids fail (20).

Cyclophosphamide, in selected cases of neurosarcoi, is a useful drug, especially if rapid onset is required (22). A 46-year-old man with bilateral eighth cranial nerve dysfunction and radiculomyelitis who progressed to complete flaccid paraplegia despite intravenous and intrathecal methylprednisolone showed dramatic response to cyclophosphamide infusion within 2 weeks (23). One study reported that cyclophosphamide controlled 9/10 (90%) of the neurosarcoi cases, which was a statistically significant benefit over corticosteroids alone (84). Another report (24) documented symptomatic improvement in
4/7 (57%) of patients with neurosarcoid treated with cyclophosphamide, and all showed improvement in magnetic resonance imaging (MRI) or cerebrospinal fluid findings. The mean prednisone dose was reduced from 42 mg to 18 mg daily. Of 17 patients with spinal cord involvement from sarcoidosis, 7/7 showed improvement with cyclophosphamide compared with 5/10 (50%) treated with methotrexate (25). Cyclophosphamide was one of the several drugs that failed to control a very aggressive case of ON (24). It did stabilize and permit some recovery in a case of bilateral ON that had progressed to blindness despite high-dose corticosteroids (Frohman, unpublished data).

Mycophenolate mofetil was first reported to be effective for pulmonary sarcoidosis (26) and subsequently has proven to be successful rescue therapy for uveitis (27,28). It may be efficacious in refractory neurosarcoid, often when other medications have been ineffective (29,30). In 1 series of 8 patients with neurosarcoid, the mean dose of prednisone was reduced from 59 mg to 6 mg (30).

Infliximab is an anti-tumor necrosis factor alpha (TNF-α) agent. Hostettler et al (31) described 16 patients with corticosteroid-resistant sarcoid treated with infliximab for at least 12 months. Six of the 11 (55%) had complete remission, and 4/11 (36%) had a partial response. In only 1 patient, the infliximab had to be discontinued due to an adverse event. Neurosarcoid has been reported to be responsive to infliximab even after resistance to multiple other agents. One patient with no light perception due to ON recovered to 20/20 (32). Like cyclophosphamide, infliximab often has rapid onset. In a report of 343 sarcoid patients, 43 patients treated with anti-TNF agents showed improved cognition compared with those treated with corticosteroids or corticosteroids and methotrexate (33). There are single-case reports of optic nerve or chiasmal involvement refractory to multiple agents in which patients improved on infliximab (34–37). While reporting 3 of their own patients with refractory neurosarcoid successfully treated with infliximab, Pereira et al (38) reviewed the literature.

**TABLE 1.** Pharmacologic agents for treatment of neuro-ophthalmic sarcoidosis

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Mechanism of Action</th>
<th>References</th>
<th>Comment</th>
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<td><strong>First-line agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Folate metabolism inhibitor</td>
<td>2,3,16–20</td>
<td>Must prescribe folate</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Alkylating agent</td>
<td>19,21–25</td>
<td></td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>Inhibitor of purine synthesis</td>
<td>26–30</td>
<td>Possibility of inducing sarcoid</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Monoclonal antibody against TNF-α</td>
<td>4,15,31–44</td>
<td>Potential tachyphylaxis raises issue of concomitant treatment with MTX or other immunosuppressant</td>
</tr>
<tr>
<td><strong>Second-line agents</strong></td>
<td></td>
<td></td>
<td></td>
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<td>Leflunomide</td>
<td>Pyrimidine synthesis inhibitor</td>
<td>45–47</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine A</td>
<td>IL-2 inhibitor, reduces T-cell activation</td>
<td>10,19,48–52</td>
<td>Not effective in pulmonary disease</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>TNF-α blocker</td>
<td>53–59</td>
<td></td>
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<tr>
<td>Azathioprine</td>
<td>Purine analog</td>
<td>12,19,60–62</td>
<td></td>
</tr>
<tr>
<td><strong>Possibly effective agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Human monoclonal IgG1 TNF-α antibody</td>
<td>63,64</td>
<td>Possibility of inducing sarcoid</td>
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<tr>
<td>Chlorambucil</td>
<td>Alkylating agent</td>
<td>62,65–67</td>
<td></td>
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<tr>
<td>Rituximab</td>
<td>Monoclonal antibody that depletes circulating B-cell lymphocytes</td>
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<td></td>
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<tr>
<td>Cladribine</td>
<td>Purine analog</td>
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<tr>
<td><strong>Agents with unproven efficacy</strong></td>
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<td></td>
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<tr>
<td>Hydroxychloroquine and chloroquine</td>
<td>Inhibition of antigen presentation and processing</td>
<td>1,71,72</td>
<td></td>
</tr>
<tr>
<td><strong>Tetracyclines</strong></td>
<td>Anti-infectious and nitric oxide synthase inhibitor</td>
<td>52,73–76</td>
<td></td>
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<tr>
<td><strong>Probably ineffective agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Inhibition of T-cell-mediated responses</td>
<td>77,78</td>
<td></td>
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<tr>
<td>Etanercept</td>
<td>TNF-α receptor blockade</td>
<td>2,79</td>
<td>Possibility of inducing sarcoid</td>
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<tr>
<td>Intravenous immunoglobulin</td>
<td>Multiple; principal action not established</td>
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and found 17 additional cases treated with infliximab. All showed clinical improvement, with adverse effects in 4/16 (23%). There are 2 particular concerns with the use of infliximab. First, tachyphylaxis may occur due to antibody formation. Concomitant immunosuppression may prevent this occurrence. Second, anti-TNF therapy can lead to autoimmune disorders such as systemic lupus erythematosus.

While unusual, patients treated with anti-TNF agents may develop sarcoidosis. Sturfelt et al (39) described a patient treated with infliximab for rheumatoid arthritis who developed neurosarcoid with papilledema, sixth nerve palsy, uveitis, and retinal periphlebitis. Removal of the drug, placement of a ventriculoperitoneal shunt, and treatment with corticosteroids and methotrexate led to resolution. Induction of what is pathologically indistinguishable from sarcoidosis with anti-TNF therapy for autoimmune diseases is not restricted to infliximab as it has been reported with entanercept (40) and adalimumab (41,42). In reviewing the literature, Tong et al (43) found 37 such cases [entanercept 22/27 (59.5%), adalimumab 5/37 (13.5%), and infliximab in 10/37 (27%)].

The cause of this phenomenon is unknown. Lamrock and Braun (44) proposed that this may be due to cytokine imbalance. Although TNF-α may suppress autoreactive T-cells, loss of this suppression may facilitate granuloma formation. In addition, entanercept increases the production of interferon-γ, which is vital for granuloma formation (83).

**Agents to Consider for Use in Refractory Neurosarcoid/Neuro-Ophthalmic Sarcoid**

Leflunomide was successfully used in a sarcoid patient with pulmonary, sinus, and cutaneous involvement who had failed the treatment with corticosteroids, azathioprine, methotrexate, and hydroxychloroquine (45). In a report of 32 patients (mainly with ocular and pulmonary disease) treated with leflunomide, 15 were also given methotrexate. Leflunomide was effective in 12/17 (71%) patients and with methotrexate in 13/15 patients (46). In another study, 76 patients were prescribed leflunomide, 86% of whom had been on another immunomodulating agent, or corticosteroids (47). Among all patients with nonpulmonary disease, 32% had a partial response. Of 8 patients with ocular involvement, 5 (62.5%) had a good response, 2 (25%) had a partial response, and 1 (12.5%) had no response, and of the 3 patients with neurosarcoid, 1 (33%) had a good response but 2 (67%) had no response.

Cyclosporine has been used in neurosarcoid with variable results (48). It was successfully used in a patient with sarcoid uveitis and ON (49). Stern et al (50) treated 6 patients with refractory neurosarcoid. Although this medication allowed a reduction in corticosteroid dose by 30–58%, 4 patients deteriorated and 1 died. Cyclosporine was shown not to be effective for pulmonary sarcoidosis in a randomized controlled trial of 37 patients (51). This resulted in abandoning cyclosporine in the treatment of all forms of sarcoid. That cyclosporine is lipid soluble, which potentially makes it attractive in patients with neurosarcoid. Yet in 1 case series, it only controlled 2/7 (29%) cases of ON (18). With questionable efficacy and significant toxicity, the role of cyclosporine in neuro-ophthalmic sarcoid remains unclear (52).

Thalidomide was reported effective in patients with refractory cutaneous sarcoid (53,54) and shown to be of benefit with paranasal sinus involvement (55). The first neurosarcoid patient treated with thalidomide had bilateral ON and had failed multiple 2 and 3 drug regimens (56). Thalidomide stabilized this patient allowing corticosteroid doses to be reduced. Although there are other reports of patients with refractory neurosarcoid who responded to thalidomide (57–59), its potential use is limited due to teratogenicity.

Azathioprine has been used effectively in cases of pulmonary sarcoid (60,61). However, there is limited literature on azathioprine use for neurosarcoid. Pawate et al (12) reported that 8/54 neurosarcoid patients were maintained on either azathioprine alone or in combination with prednisone. Azathioprine was successfully used in 2 patients with neurosarcoid with ON after treatment with corticosteroids and RT was unsuccessful (62), but in another report it failed in patients with refractory ON.

**Agents With Possible Efficacy in Refractory Neurosarcoid/Neuro-Ophthalmic Sarcoid**

Adalimumab has been shown to be effective in refractory sarcoid uveitis (63). It also has been used successfully in a patient with neurosarcoid resistant to a combination of corticosteroids and methotrexate (64).

Rituximab has had limited use in sarcoid and neurosarcoid. It did control 1 patient with neurosarcoid who had been resistant to corticosteroids, cyclophosphamide, and methotrexate (68,69).

Chlorambucil was used in 10 cases of pulmonary sarcoid after failing the treatment with corticosteroids, of whom 8 patients (80%) showed improvement (65). In 31 patients with refractory systemic sarcoidosis treated with chlorambucil, marked improvement was seen in 15/31 (48%) and 13/31 (42%) showed moderate improvement. However, patients often relapsed with drug withdrawal (66). A case of orbital sarcoidosis with proptosis and ophthalmoplegia that responded to chlorambucil and corticosteroids has been reported (67) as well as a patient refractory to corticosteroids and RT whose chiasmal sarcoidosis responded to treatment with chlorambucil (62).

Cldarabine was used in a patient with sarcoid ON who was refractory to cyclosporine and cyclophosphamide (70).
The visual loss recurred within a year of the completion of cladribine therapy, but recovered when this medication was restarted.

Agents Effective in Some Forms of Sarcoid, Yet, Are Untested/Unproven in Neurosarcoid/Neuro-Ophthalmic Sarcoid

Chloroquine may be effective as maintenance therapy in patients with pulmonary sarcoidosis. One purported etiology of sarcoidosis is altered immunity to Propionibacterium acnes. A subset of patients with sarcoid are sensitive to tetracyclines, which are effective against P. acnes. Minocycline has anti-inflammatory and antibacterial properties. Its use in cutaneous sarcoid has been reported. Others have documented its success in cases with ocular or orbital involvement. Its use in neurosarcoid has not been reported. Caution is needed to avoid a potentially life-threatening Jarisch–Herxheimer reaction that may occur when patients with sarcoid are treated with antibiotics.

Agents without established efficacy in neurosarcoid/neuro-ophthalmic sarcoid are listed in the Table.

Combination Drug Therapies

When a patient fails corticosteroid therapy, there are no established guidelines to institute a second or multidrug regimen. Moravan and Segal reported 6 patients with neurosarcoid refractory to corticosteroids who were treated with infliximab and mycophenolate mofetil. All demonstrated clinical improvement by the fourth course of infliximab, and all showed improvement on MRI scan of the brain. No significant side effects were seen in the follow-up period. When deciding to institute multidrug therapy, it is best to individualize treatment with consideration of factors such as rapidity of onset and side effects of each medication.

Radiation Therapy

RT generally is reserved for patients who fail medical therapy. Gelwan et al treated 4 patients with ON with radiation who did not respond to steroid therapy. Although there was a transient improvement, visual loss recurred within 3 months. Others have reported single cases in which RT was beneficial. A literature review on the use of radiotherapy for refractory neurosarcoid concluded that such therapy might stop disease progression, but would not likely restore function.

TREATMENT GUIDELINES

Terushkin et al published a neurosarcoid treatment strategy, suggesting mycophenolate mofetil for patients with severe disease who fail corticosteroids and do not need rapid therapeutic effect, and infliximab with cyclophosphamide as an option for those requiring rapid onset. For mild to moderate cases failing corticosteroids, they propose mycophenolate mofetil, methotrexate, azathioprine, or hydroxychloroquine, and possibly RT. Terushkin et al propose that symptomatic cases of neurosarcoid may be treated with either corticosteroids or hydroxychloroquine.

For neuro-ophthalmic sarcoid, we recommend an approach similar to Baughman et al; either intravenous or high-dose oral corticosteroids as initial therapy, which is tapered after 4–6 weeks. If corticosteroids fail, consider adding mycophenolate mofetil, azathioprine, or methotrexate as a second agent. Once on a second agent, attempt to taper the patient off corticosteroids. If this cannot be accomplished, a third medication may be added, either anti-TNF agent or intravenous cyclophosphamide.

Our specific treatment regimen for neuro-ophthalmic sarcoid (Fig. 1) is to prescribe patients with acute severe disease 1 g of solumedrol daily in divided doses for 3–5 days, followed by 1 mg/kg of oral prednisone. Less acute cases may be started on 1.0 mg/kg of oral prednisone. If there is favorable response after the first month, we begin a 3–6 month corticosteroid taper. If the patient had a favorable response to corticosteroids, but worsens with taper, rather than start a second agent, we may repulse with intravenous corticosteroids, followed by slower taper of oral corticosteroids over approximately 1 year.

If a rapid clinical response is needed, we begin a second agent, either intravenous cyclophosphamide or infliximab. We recommend that the dosing and monitoring for side effects not be performed by the neuro-ophthalmologist alone, but rather by rheumatologist, oncologist, or other physician familiar with these medications. When cyclophosphamide is selected, Doty et al propose the following regimen: intravenous cyclophosphamide initially at a dose of 500 mg, then 750 mg for the second dose, and a maintenance dose of 1 g. After 5 doses, treatment is reevaluated, and if possible, a less toxic drug used.

If infliximab is selected, Moravan and Segal propose that the patient receives 5 mg/kg intravenously every 2 weeks for a total of 3 doses. This dose is repeated every 5–6 weeks as maintenance therapy but a decision will have to be made about the possibility of tachyphylaxis.

In some patients, retreatment with intravenous corticosteroids may have sufficient therapeutic effect that a second agent with slower onset may be used. In this case, we typically use methotrexate, as it is relatively well tolerated. Generally, we start with a dose of 10 mg weekly. The patient’s white cell count must be monitored, and folate is given concurrently.
Mycofenolate mofetil also is well tolerated and often used if methotrexate is ineffective. The initial dose is 500 mg twice daily and is gradually increased to 1 g twice daily as tolerated (30,89). However, a major concern is the risk of progressive multifocal leukoencephalopathy (91). Patients who fail methotrexate and mycofenolate mofetil may be offered infliximab or cyclophosphamide, mindful that infliximab could potentially worsen the disease.

With a patient on 2 medications that are controlling disease, we maintain the corticosteroid dose at 0.5–1 mg/kg for 1 month and then begin to taper corticosteroids over 3–6 months. If this is successful, we maintain the patient on the single immunosuppressant for 12 months, and if the clinical and neuroimaging results are favorable, taper the drug over the ensuing 6 months. In the patient who flares with corticosteroid taper while also on an immunosuppressant, or flares after the corticosteroids are withdrawn and they are on immunosuppressant alone, the flare tells us that the immunosuppressant was not adequately suppressing disease activity. The option then is to repulse with steroids and begin the process again, knowing that the patient may require long-term maintenance on an immunosuppressive agent, or to restart the process with a new intravenous steroid bolus, but trying a different immunosuppressive medication. Failure at this point likely requires a 3-drug regimen or possibly radiotherapy.

REFERENCES


Diagnostic Tests for Concussion: Is Vision Part of the Puzzle?

Rachel E. Ventura, MD, PhD, Jeffrey M. Jancuska, BA, Laura J. Balcer, MD, MSCE, Steven L. Galetta, MD

Background: Concussion, particularly in relation to sports and combat activities, is increasingly recognized as a potential cause of both short- and long-term neurologic sequelae. This review will focus on the neuro-ophthalmologic findings associated with concussion, the current tests for concussion, and the potential for visual performance measures to improve our detection and assessment of concussions.

Evidence Acquisition: A PubMed search using the specific key words “concussion,” “mild traumatic brain injury,” “neuro-ophthalmological findings,” and “diagnostic and management tests” was performed. An emphasis was placed on articles published during the past 5 years, but additional articles referenced within recent publications were obtained.

Results: Concussion is frequently associated with abnormalities of saccades, pursuit eye movements, convergence, accommodation, and the vestibulo-ocular reflex. Current sideline testing for athletes includes the Sports Concussion Assessment Tool, Third Edition (SCAT3) incorporates cognitive and balance testing. The King–Devick (K–D) test is a rapid visual performance measure that can be used on sidelines by nonmedical personnel, including parents of youth athletes. The K–D test complements components of the SCAT3 and improves the detection of concussions. Other vision-based tools for diagnosing and for managing concussion include eye movement tracking devices, pupilary assessment, computerized testing, imaging modalities, and electrophysiologic testing. Many of the imaging modalities and electrophysiologic studies have been combined with vision-based tests.

Conclusions: Concussion is associated with many neuro-ophthalmologic signs and symptoms. Visual performance measures enhance the detection and management of concussion, and future studies are under way to further incorporate vision-based testing into sideline diagnosis and long-term clinical assessments.

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Traumatic brain injury (TBI) is a major cause of morbidity and mortality worldwide. The Centers for Disease Control and Prevention have estimated that there are between 1.4 and 3.8 million sports-related mild traumatic brain injuries (mTBI) annually in the United States alone, although this approximation is based on emergency room rather than outpatient visits (1–3). Concussion, a mild form of mTBI (4) (Table 1), remains underreported based on anonymous surveys of collegiate athletes (6), in part reflecting a misconception that concussion is a benign brain injury.

Concussion is defined as a direct or indirect impulse to the head or body with accompanying neurological symptoms (7, 8). Visual complaints are especially common in concussion (see Supplemental Digital Content, Table E1, http://links.lww.com/WNO/A135). Sustaining one concussion increases the risk of the second concussion in the same season by threefold (9) and concussed athletes who return to play before complete recovery are vulnerable to the rare, but potentially catastrophic second impact syndrome (9–11). Concussion has also been associated with long-term sequelae including neurodegenerative disorders (12–14). Given that concussions may have devastating short- and long-term effects, tools that improve our assessment and management are critical.

We will first explore deficits in visual function after concussion, which can help in both screening and monitoring the recovery of TBI symptoms. Then, we will review the most widely used concussion tests, some of which are now vision-based.
VISUAL FUNCTION DEFICITS IN CONCUSSION

The cognitive control of eye movements requires pathways involving fronto-parietal circuits and subcortical nuclei (15), many of which are particularly vulnerable to concussion. Common neuro-ophthalmic findings in concussion include abnormalities in saccades/antisaccades, smooth pursuit, vergence, accommodation, the vestibulo-ocular reflex, and photosensitivity (Table 2). In the first 10 days after mTBI, patients have been found to have impaired antisaccades, prolonged saccadic latencies, higher directional errors, poorer spatial accuracy, and impaired memory-guided saccades (16,17). Patients with postconcussive syndrome 3–5 months after their injury perform worse on antisaccade testing, memory-guided saccades, and a self-paced saccade test in which subjects look back and forth between two points as rapidly as possible, when compared with patients who have had mTBI and recovered well (18). In addition, the gap saccade test has been studied in which subjects fixate on a central target and then, after varying amounts of time, fixate on a peripheral target. Patients with acute mTBI had longer saccadic reaction times when there is a short temporal gap between the central and peripheral targets, but not when the temporal gap is longer, suggesting difficulties in disengaging attention (19). These studies demonstrate abnormalities in saccadic function with concussion that, in part, relate to impairments in executive function (as probed with antisaccade tests), attention (as with the gap saccade test), and memory (as with memory-guided saccade tests) (Table 2) (16–20). Symptom resolution often corresponds with return of normal saccadic function (18). These saccadic tests have been studied in the research setting and require the use of a computer and video-oculography and thus have limited clinical application at this time. The absence of baseline testing, calibration issues, poor attention, and medication effects could be other issues that complicate the routine testing of eye movements.

Saccadic dysfunction as assessed clinically may be present in approximately 30% of patients with mTBI (21). Smooth pursuit requires attention, anticipation, and working memory as well as smooth and at times, saccadic eye movements to fixate on a moving target (22). Suh and colleagues (23,24) correlated mTBI with decreased target prediction, increased eye position error, and variability of eye position using a circular tracking test. Temporarily extinguishing the target, which necessitates more predictive tracking, resulted in more abnormal findings. When tested clinically, it was found that 60% of mTBI patients had abnormalities in pursuit eye movements (21).

Convergence abnormalities have been reported in 47%–64% of patients with concussion (21,25). Additionally, 65% of concussed patients vs. only 15% of controls have abnormalities in accommodative amplitude (21). Patients with sports-related concussions often have symptomatic complaints attributable to either convergence or accommodative insufficiency, such as headaches, “sore eyes,” words coming in and out of focus, and losing one’s place while reading (21). Peripheral and central mechanisms of vertigo also commonly occur with concussions. In addition, patients often complain of increased light sensitivity, which is possibly due to meningeal irritation, migraine, or driven through central pathways such as the thalamus (26). Ocular motor palsies and other cranial nerve abnormalities are unlikely to occur in concussion as opposed to more severe forms of TBI, and their presence with concussion should alert the examiner to look for a preexisting structural abnormality such as an arteriovenous malformation, aneurysm, or tumor (27).

Testing individual eye movements is important, but requires clinical expertise which may limit widespread use on the sideline, particularly at the youth level where sports parents will be in charge of concussion assessment. Cost, standardization, accessibility, and reliability will be other considerations when developing sideline tools for concussion evaluation.
CONCUSSION TESTS

Concussion tests can be divided into those used for diagnosis and initial assessment, including symptom checklists and sideline evaluations, and those used for management, including computerized neurocognitive testing, neuroimaging, biomarkers, and electrophysiology.

Symptom Checklists

Symptom checklists rely on self-reporting among a list of symptoms (see Supplemental Digital Content, Table E2, http://links.lww.com/WNO/A136) and as such are susceptible to underreporting (28). In an online survey of 262 University of Pennsylvania athletes, 43% of participants with a history of concussion have hidden symptoms to stay in a game (6). Apart from suffering from potentially inaccurate reporting, symptom checklists may have a limited role in return-to-play guidelines because cognitive impairment may persist beyond symptom resolution (29), although they are helpful in monitoring recovery. Mucha and colleagues (30) have recently described a screening test, called the Vestibular/Ocular Motor Screening Assessment, in which symptoms are reported while subjects undergo a battery of vestibular and ocular provocations. They found that subjects who reported symptoms with the provocations of undergoing vestibular–ocular reflex testing or testing visual motion sensitivity were highly likely to be in the concussed group with an odds ratio of 3.89 and 3.37, respectively. Thus provoked symptoms may be a more accurate way to assess patients with possible concussions, but this methodology still suffers from biases inherent in patient self-reporting. Combining provoked symptoms with any objective findings on the vestibular and ocular examination may increase the likelihood of predicting subjects with concussion and also provide clues regarding inaccurate reporting.

Sideline Tests

King–Devick (K–D) Test

Since approximately 50% of the brain’s circuits are related to vision (31), and many of these pathways are susceptible to injury in concussion, performance measures involving visual function are promising in sideline assessment. To perform the K–D test, the subject rapidly reads numbers on three test cards, with the score being the total time required in seconds (see Supplemental Digital Content, Figure E1, http://links.lww.com/WNO/A133). This typically takes 1–2 minutes. Rapid number naming requires a distributed network of saccade areas including those in the
dorsolateral prefrontal cortex (DLPFC) that are responsible for anticipatory saccades (15,32). The K-D test also requires attention and language, as well as other areas involved in reading; K-D thereby tests functioning of the brainstem, cerebellum, and cerebral cortex (33,34). Eye movement abnormalities commonly occur with concussion and the K-D test allows them to be assessed without the clinical expertise that would otherwise be required. Like any functional test, K-D baseline scores can be potentially limited by those athletes who will fully attempt to sandbag the test. Understanding the typical range of scores and encouraging the athlete to read as fast as they can limit such activity. Factors that may limit sandbagging of functional tests is an important area for future investigation.

Studies of mixed martial arts fighters, boxers, collegiate athletes, professional hockey players, and rugby players consistently reveal an average 5- to 7-second increase (worse) score immediately after concussion compared with baseline (33–36). Any worsening of the K-D score from baseline suggests the presence of a concussion (33–36). Scores are not worsened by routine exercise, and there is a learning effect with repeated testing (33). Furthermore, a control cohort studied at the same time as the concussed athlete group showed an improvement of K-D times. Given that other sideline tests such as the Standardized Assessment of Concussion (SAC) and Balance Error Scoring System (BESS; see below) do not assess eye movements, we studied whether the K-D would provide additional information in a cohort of University of Florida athletes (5). We found that the SAC and BESS even when used together as sideline tools failed to show abnormalities in 10% of the 20 concussions under study. With the addition of the K-D, all of the concussions could be identified. Thus, adding the K-D increased our ability to detect concussed athletes and complements the SAC and BESS as a performance measure.

**Sport Concussion Assessment Tool, Third Edition (SCAT3)**

The SCAT3 is a commonly used sideline tool that consists of a 22-item symptom checklist, cognitive and physical examination, the Glasgow Coma Scale, Maddocks questions (set of 5 questions that assess game-specific orientation and recent memory) (37, 38), the modified BESS, and the SAC. The SCAT3 takes 15–20 minutes to complete and was compiled by a consensus committee based on best available measures (39). A composite score reflects the quantity of questions in each section rather than the importance and may not be as helpful as using each component alone (39). Baseline testing is required due to individual variability (40–42). The SCAT3 does not test all areas, such as vision, limiting its use as a sole indicator for concussion diagnosis or for return-to-play, although it can provide supportive information (43). The lack of a vision test in the SCAT3 is a current gap despite its widespread use a sideline concussion tool.

**Standardized Assessment of Concussion**

The SAC is a component of SCAT3 that measures cognitive areas including orientation, immediate memory, concentration, and delayed recall (Fig. 1) (44–48). In one study, only 50% of 28 concussed collegiate athletes had abnormal SAC testing. The test was able to capture some concussed athletes with normal BESS and K-D scores and seems to have value as a complementary test (5). One should note that the scores may be artificially inflated since athletes can memorize sections of the test (49).

**Balance Error Scoring System and Other Tests of Balance**

The BESS, another component of the SCAT3, tests balance (see Supplemental Digital Content, Figure E2, http://links.lww.com/WNO/A134). Likely due to its subjective nature, there is a high variability in scoring for the BESS. The inter-rater reliability intraclass correlation (ICC) has been reported as 0.57, with intrarater reliability ICC’s of 0.74 (50). Given this variability, particularly between raters, it is prudent to have the same individual measure baseline and postconcussive BESS scores when possible. Performance on the BESS also can vary over the course of the season, as it is affected by the sport played, history of ankle injury, and fatigue (51–55).

**Components of the Standardized Assessment of Concussion Test**

**Orientation (1 point for each correct answer, 5 possible points total)**

- What month is it?
- What is the date today?
- What is the day of the week?
- What year is it?
- What time is it right now? (within 1 hour)

**Immediate memory (1 point for stating each of 5 words over 3 trials for a total of 15 possible points)**

- Alternate words:
  - Elbow: candle
  - Apple: paper
  - Carpet: sugar
  - Saddle: sandwich
  - Bubble: wagon

**Concentration: Digits Backward (1 point for completing each of the digit series backwards, for a total of 4 possible points)**

- Alternate digit list:
  - 4-9-3: 6-2-9
  - 3-8-1-4: 3-2-7-9
  - 6-2-9-7-1: 1-5-2-8-6
  - 7-1-8-4-6-2: 5-3-9-1-4-8

**Concentration: Months in Reverse Order (1 point for entire sequence correct)**


**Delayed Recall (total possible 5 points)**

**FIG. 1.** Standardized assessment of concussion test examines orientation, memory, and concentration function (42). Total possible of 30 points.
Portable inertia sensors may help to obtain more objective and sensitive measures of balance. One study found that although the BESS alone could not distinguish controls from those with a recent history of concussion and balance complaints, the addition of a portable inertia sensor enabled detection of significant differences (56). Additionally, Wii Balance Boards provide another objective balance test and have been shown to have improved validity (0.99) and test–retest reliability (0.88) over the BESS (57).

**Head Impact Telemetry System**
Head impact telemetry system is an investigational tool in which a series of accelerometers incorporated into the padding of a football helmet provide data on the magnitude and location of impact (58). Factors such as a rotational acceleration greater than 5500 radians per second, linear acceleration greater than approximately 96 g, and location of impact can be predictive for concussion (58). By analyzing these measurements on the field, athletes at risk for concussive injury could potentially be identified, many of whom may show evidence of structural compromise using diffusion tensor imaging (DTI) even without a clinical presentation (59). Individuals with impacts below the predicted concussion threshold can still have a concussion, making complementary assessments necessary (49).

**Eye Movement Tracking Devices**
Use of a portable head-mounted video-based eye tracker to detect abnormalities in eye movements has been studied in the research setting on a limited basis. Cifu and colleagues (60) recently reported use of an eye tracking device on 60 military subjects with persistent concussive symptoms vs. 26 controls and found that those with the concussive symptoms had significantly larger saccadic position errors, smaller saccadic amplitudes, smaller predicted peak velocities, smaller peak accelerations, and also abnormalities in pursuit velocities. Further work is required to determine how acutely these eye movement changes occur and the exact time course for recovery.

**Immediate Postconcussion Assessment Cognitive Test and Other Computerized Neurocognitive Tests**
Immediate postconcussion assessment cognitive test (ImPACT) is a computerized neuropsychological test battery that takes 20 minutes to complete. Deficits detected by ImPACT correlate with traditional neuropsychological testing (61) and with functional magnetic resonance imaging (fMRI) findings such as altered activation of the DLPFC (62). Visual subscores on ImPACT correlate with the K–D test (5). The software incorporates statistical techniques to account for normal test score variability over time and can usually detect intentional “sandbagging” by flagging athletes with scores on certain subscales that are below predefined values (63,64). Meaningful postinjury ImPACT results require baseline testing (65,66), since factors such as attention-deficit hyperactivity disorder and learning disabilities affect baseline scores (67). Eighty-three percent of athletes with concussion who completed the ImPACT battery did show cognitive impairment, although it is notable that 17% of those with concussion did not show any abnormality on the cognitive measures (68) and that up to 20%–40% of nonconcussed athletes demonstrated cognitive impairment (61,69,70). One should be cautious in the use of ImPACT in return-to-play decisions, given insufficient validity and test–retest reliability, and also because subjects may have ongoing metabolic abnormalities in spite of return of ImPACT scores to baseline (71). Other computerized programs have emerged, and further study of their ability to detect and guide return to play need to be performed. Computerized testing has its limitations and should be used by those skilled in the interpretation of such testing.

**Neuroimaging**

**Conventional Magnetic Resonance Imaging and Computed Tomography**
A commonly accepted definition of mTBI/concussion requires normal computed tomography imaging. Routine magnetic resonance imaging (MRI) is often normal as well (72,73), although susceptibility-weighted imaging sequences can detect microhemorrhages associated with subconcussive or concussive injury (74). One prospective study found that 4 of 19 patients with mTBI had brain atrophy as measured by MRI volumetry 3–7 months postinjury. However, this was a small study, and it did not include patients with sports-related concussions (75). Another study found that collegiate football players had decreased hippocampal volumes vs. controls, with an inverse relationship between left hippocampal volume and years of football played (76). Among the football players, those with a history of concussion had the smallest hippocampi (76).

**Diffusion tensor imaging**
DTI maps the diffusion of molecules, mainly water (77). Fractional anisotropy is a measurement of the fraction of diffusion magnitude (78) and has been shown to be a reliable marker of white-matter integrity (72,79). Significant DTI findings in players with a history of concussion compared with nonconcussed controls include widespread increase in fractional anisotropy and decreased trace and radial diffusivity in the right corona radiata, right posterior limb of the internal capsule, right superior temporal white matter (80), and optic radiations (81).

Maruta and colleagues (73) used video-oculography to record visual tracking of a moving target in a circular trajectory combined with DTI analysis of their concussed subjects. They found that large gaze error variability was
associated with low fractional anisotropy values in areas known to be frequently compromised in concussion, such as the right anterior corona radiata, the left superior cerebellar peduncle, the genu of the corpus callosum, and a number of other brain regions.

DTI also has been studied in subjects with subconcussive impacts. In one study, nonconcussed athletes in contact sports were found to have significant changes in mean diffusivity in the corpus callosum and fractional anisotropy in the amygdala when compared with athletes in noncontact sports over the course of one season. Measurements of head impact detected with a helmet sensor correlated with changes in white-matter diffusivity in several brain regions, in spite of not having a clinical concussion (59). These studies highlight a role for DTI in further delineating the pathology associated with concussive or subconcussive brain injuries.

**Functional Magnetic Resonance Imaging**

Blood-oxygen-level-dependent (BOLD) MRI detects changes in the oxygenation state of hemoglobin, thereby capturing oxygen consumption associated with neuronal activation (79). With concussion, changes in brain activation using fMRI are observed acutely and several months after injury even without clinical changes (82–87). Patients with severe postconcussion symptoms have increased activity in the normal working memory network that correlates with symptom severity (88,89). Conversely, patients with concussion have reduced activation in the DLPFC, insular cortex, anterior cingulate cortex, striatum, and medial frontal and temporal regions (90). Functional MRI studies on mTBI patients with concussion who were performing a visual working memory task showed decreased BOLD signal intensities in the right mid-DLPFC, which corresponded to severity of their postconcussive symptoms (91). However, one caveat is that it can be challenging to interpret fMRI changes given the complexity of neuronal circuitry (92).

**Magnetic Resonance Spectroscopy**

Magnetic resonance spectroscopy (MRS) measures the concentrations of molecules associated with brain metabolism (72,79). Concussion significantly lowers levels of gray matter glutamine and N-acetylaspartate (NAA) and increases levels of white matter creatine (Cr) and choline (Cho) (72,93,94). MRS studies on one cohort of patients with concussion who had symptom resolution in about 3 days found that it took 30 days for the NAA level and NAA/Cr ratio to return to baseline (94). Another study of patients with concussion who required about 15 days for symptomatic clinical recovery found that it took 45 days for the NAA/Cho ratio to return to baseline (95). MRS holds promise clinically in determining metabolic recovery from concussion and aiding in return-to-play decisions (94).

**Positron Emission Tomography**

Positron emission tomography (PET) scanning uses radio-labeled metabolic analogs to measure the rate of brain glucose metabolism (72,79). Mild TBI decreases glucose metabolism in the cerebellar vermis, pons, and medial temporal cortex (96). Decreases in glucose metabolism in concussed patients were found to correlate with cognitive disturbances (97). Further research is necessary to validate these studies and determine the potential clinical utility of PET scanning, with the ultimate goal of identifying individuals at risk for worse outcomes or neurodegeneration (98).

**Electrophysiology**

Concussion leads to abnormal electrical activity, such as smaller amplitudes of frontal N350 and parietal P300 evoked responses (99,100). Patients with multiple concussions have been found to have abnormal electrophysiological results even 2–3 years after their last injury, well after symptoms have resolved. This has been shown when patients perform a visual spatial attention and short-term memory task (101). Electrophysiological techniques, particularly when paired with visual tasks, provide insight into subclinical postconcussive abnormalities and may help to predict those vulnerable to long-term sequelae.

**CONCLUSIONS**

Concussion and mTBI have a multitude of effects on the visual system, necessitating a careful neuro-ophthalmic examination. Clinically, tests of saccades, pursuit, convergence, accommodation, vestibular–ocular reflex, and ocular misalignment are frequently abnormal. Sideline tests of visual performance, such as the K–D test, may be a sensitive means of screening for sports-related concussion. As a visual performance measure with an objective end point, this tool can be administered at the sideline by a nonprofessional.

The armamentarium for assessing concussion is largely under development. Tests under exploration for assessing long-term sequelae of mTBI include ocular coherence tomography, as it has been found that mice with blast injury have a decrease in the retinal nerve fiber layer 3 months postinjury (102). Other devices measuring afferent and efferent visual dysfunction are currently being developed, but their cost, efficiency, and need for expert interpretation may limit their widespread use.

Vision has also garnered attention for potential use in predicting subjects at risk of more severe head impacts. Harpham and colleagues (103) found that those athletes with low visual and sensory performance, including on such tasks as depth perception and visual reaction time, had a higher number of more severe impacts measured using head impact telemetry. This raises the question as to whether visual training can decrease the likelihood of severe head impacts, and further study in this area is ongoing.
We have highlighted the merits of many of the currently used tests, but, at present, there is no single test that alone can reliably diagnose concussion or determine when recovery has occurred. Clinical decision making based on examination and assessment of a wide variety of tools is still necessary. Given the potentially devastating long-term effects of repeated head trauma, it is important to be able to accurately assess even subclinical brain injury. A combination of visual processing tasks, neuroimaging, serum biomarkers, and electrophysiological recordings may allow further insights into subtle damage that has occurred from concussion and future clinical implications.

STATEMENT OF AUTHORSHIP

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Wear and Tear Vision

Konrad P. Weber, MD, Caterina Schweier, MD, Veronika Kana, MD, PhD, Thomas Guggi, MD, Katarzyna Byber, MD, Klara Landau, MD, FEBO

Dr. Weber:

A 66-year-old woman was referred to the neuro-ophthalmology unit with a 4-month history of insidious unexplained bilateral visual loss. Ophthalmologic examination revealed visual acuity of finger counting in both eyes. Confrontation visual field testing demonstrated bilateral central scotomas with relative sparing of the peripheral fields. There was a mild right relative afferent pupillary defect. The optic discs and macule appeared normal. Specifically, there was no optic disc pallor or swelling.

The patient’s medical history was significant for coronary artery disease associated with myocardial hypertrophy and for treated secondary hypothyroidism after a subtotal thyroidectomy for benign nodular disease at age 44 years. Previous surgeries included bilateral hip replacements with revision on the left side 1.5 years before consultation and a right carotid endarterectomy for a 95% stenosis 3 months before consultation. Ophthalmologic history revealed laser photocoagulation for a retinal tear in her right eye. Review of systems revealed recurrent depression, fatigue, and bilateral hearing loss. She was a smoker of 10 pack-years.

At the time we examined the patient, she had already undergone brain magnetic resonance imaging (MRI), which did not reveal an explanation for her visual loss. We performed orbital MRI, with both unenhanced and contrast-enhanced sequences that showed no abnormalities either. Based on the clinical findings of profound bilateral visual loss for 4 months associated with bilateral central scotomas and a normal fundus examination, normal neuroimaging, and significant constitutional symptoms, we suspected that the patient had paraneoplastic retinopathy, such as cancer-associated retinopathy (CAR) or melanoma-associated retinopathy (MAR). A full-field electroretinogram (ERG) according to ISCEV standards revealed severe cone dysfunction (amplitude of single flash b-wave and 30-Hz flicker response reduced to 20%–30% of the normal mean) and low normal rod function (amplitude of the b-wave reduced to 30%–40% of the normal mean).

Dr. Landau:

In view of the ERG findings that seemed to be consistent with a paraneoplastic retinopathy, we referred the patient for a systemic evaluation.

Dr. Weber:

An extensive workup revealed no evidence of malignancy. In addition, an assay for antirecoverin antibodies for CAR was negative, as were assays for a variety of anti-central nervous system antibodies, including Hu, Ri, Yo, Amphiphysin, CV2, Ta/Ma2, and Ma. A complete blood count was normal except for polycythemia with hemoglobin of 125 g/L (normal: 117–153 g/L). Serum vitamin B12 concentration was normal. The erythrocyte sedimentation rate was 2 mm/h, and autoimmune screening including ANA, ANCA, anti-SS-A, and anti-SS-B revealed no abnormalities. Both gynecologic and dermatologic examinations were nonrevealing. A FDG-PET-CT showed inflammation of the left hip consistent with bursitis. We elected to follow the patient; however, she was lost to follow-up.

T. Guggi:

Two years later, the patient was examined in our orthopedic clinic for chronic left hip pain and muscle tenderness that had persisted after the replacement of a fractured ceramic head 3 years earlier. Radiography of the left hip revealed what appeared to be metallic debris around the prosthesis (Fig. 1). Consequently, the patient underwent revision of the prosthesis. After removal of the cup and the deteriorated metal head, the site was thoroughly debrided. A new cup with a cross-linked polyethylene insert was implanted, and a ceramic head with metal head adapter replaced the removed metal head. The original stem was left in place. On inspection at the time of surgery, the retrieved metal head was worn down (Fig. 2), and there was a significant...
amount of metallic debris surrounding the prosthesis (Fig. 3). A blood test was performed.

**Dr. Byber:**

The blood test was an assay for serum cobalt. This revealed an extremely elevated serum cobalt level of 6975 nmol/L (normal: < 17 nmol/L), so that a diagnosis of cobalt neurotoxicity was made. After surgery, cobalt levels exponentially dropped to 1220 nmol/L within 40 days and to 136 nmol/L within a year, approaching the reference value of 119 nmol/L for patients with metal implants. This decrease corresponded well to the known toxicokinetics of the metal (1), consistent with the hypothesis that the defective prosthesis was the cause for the elevated cobalt level.

**Final Diagnosis**

Cobalt neurotoxicity from abraded metallic hip prosthesis.

**Dr. Weber:**

After removal of the prosthesis, the patient’s hip pain slowly improved such that she was able to walk without discomfort. Her hearing, which had been slowly worsening while the damaged prosthesis was in place, also improved (Fig. 4). Unfortunately, her visual acuity did not improve remaining finger counting in each eye.

**Dr. Weber and Dr. Landau:**

In our patient’s case, cobalt neurotoxicity caused devastating visual loss accompanied by a dramatic deterioration of the patient’s general condition triggered by a mechanical orthopedic problem. Over the last few years, reports of cobalt toxicity related to hip implants have attracted increasing medical attention (2,3) as exemplified in the television program “House” (4). In terms of visual loss, case reports suggest that cobalt poisoning may induce toxic effects in both retinal ganglion cells and optic nerve axons (5,6). In our patient, the retinopathy was the cardinal symptom, whereas the optic neuropathy only became apparent on follow-up. The toxicity seems to be caused primarily through interaction of free Co(II) ions with various metabolic processes (1). Interestingly, cobalt chloride has been used as an hypoxia-mimicking agent in a murine model of retinal photoreceptor cell degeneration (7).

Cobalt alloys have been widely used as implant materials for more than 80 years due to their high specific strength. Rarely, patients with metal-containing prostheses develop metallosis, a local reaction of soft tissue surrounding the implant that is characterized by the formation of a black-

**FIG. 1.** A. Radiology of the left hip shows a fractured ceramic head (arrowhead) prompting revision of the prosthesis. B. During revision, the ceramic head was replaced with a CoCrMo metal head (arrow) and a new polyethylene liner (arrowhead). C. Radiography obtained for chronic hip pain 3 years later reveals a worn-down metal head (black arrowhead) with radiopaque debris (white arrowheads).

**FIG. 2.** A. Worn-down CoCrMo metal head of the implanted hip prosthesis compared with a new metal head (B), of the same type. C. Worn-down polyethylene inlay with ceramic particles imprinted in the cavity. D. Imprinted ceramic splinters on the polyethylene inlay in the area indicated in (C), creating an abrasive surface.

**FIG. 3.** Surgical site during revision of the left hip reveals significant metallic debris around the prosthesis.
stained “pseudotumor” (8). In our case, the circumstances leading to the toxic metallosis in the hip were explained by the sequence of implants used (9) (Fig. 1). Initially, the hip prosthesis was revised because of a fracture of the ceramic femoral head (10). The ceramic head was replaced with a metal head paired with a polyethylene inlay. Subsequently, fine ceramic particles left behind from the broken head adhered to the polyethylene inlay and grinded down the new metal head like a grindstone (Fig. 2 and Supplemental Digital Content, Fig. E1, http://links.lww.com/WNO/A132). The combination of incompatible implants violated a major rule for orthopedic surgeons: never mix but always match orthopedic components (11).

In hindsight, the deterioration of the patient’s general condition, including many of her varied symptoms and signs, were attributable to cobalt toxicity (1). The patient not only experienced vision loss but also had both hearing impairment and imbalance, both of which improved after replacement of the prosthesis (Figs. 4 and 5). Although the patient was never formally tested, her acral paresthesias may have been due to a cobalt-induced polyneuropathy.

Two helpful laboratory signs of cobalt toxicity are polycythemia and hypothyroidism, both of which were present in our patient (although the hypothyroidism may have been related solely to her previous thyroidectomy). Polycythemia seems to be a particularly sensitive laboratory parameter for this condition (8), as it is rarely present otherwise in elderly patients with hip implants. Therefore, it may be helpful to test for polycythemia in patients with cobalt-containing implants.

Neurological complications from elevated cobalt levels in patients with orthopedic implants are rare. In previous reports (5,6), cobalt concentrations varied between 2074 nmol/L (serum measurements) and 10,625 nmol/L (whole blood measurements). Cobalt concentrations can be measured in serum or in whole blood; however, in patients with long-term exposure, the serum and blood cobalt concentrations will be dissimilar, as the metal ions are incorporated into the red blood cells (8). Therefore, whole blood measurements should be performed in such cases, as they are more representative of the actual cobalt level.

Our patient had a hypertrophic cardiomyopathy associated with congestive heart failure and a pericardial effusion. Two years after the initial left hip revision, she had undergone a muscle biopsy from the right ventricle that showed cardiomyocyte degeneration and atrophy as well as

![FIG. 4. Sequential audiograms show severe bilateral hearing loss with some recovery after replacement of hip prosthesis. Hearing loss 24 months before left hip revision: right = 7%, left = 9%; hearing loss 18 months after left hip revision: right = 61% left = 66%; hearing loss 9 months after replacement of left hip prosthesis right = 47%, left = 28% (results according to Current Procedural Terminology of the American Medical Association).](image)

![FIG. 5. Video head impulse test obtained 1.5 years after replacement of left hip prosthesis demonstrates bilaterally reduced vestibulo-ocular reflex gains (normal gain >0.8) with compensatory catch-up saccades (purple spikes) in response to head rotations to either side indicating involvement of the vestibular system.](image)
mild fibrosis (Fig. 6). As these findings were nonspecific (12), the suspicion of cobalt cardiac toxicity was not raised at that time; however, in retrospect, it, too, was caused by cobalt toxicity. The peculiar cobalt-induced cardiomyopathy observed in our patient first came to medical attention as “Quebec beer drinker’s cardiomyopathy” (13). In 1965, the addition of cobalt sulfate as a foam stabilizer in beer triggered an epidemic of 48 cases of cardiomyopathy associated with acute congestive heart failure within 9 months. The epidemic only affected heavy beer drinkers (3–6 L/d) of a particular brand and individuals with poor nutritional status. Interestingly, in this acute setting with a mortality of 40%, visual loss did not occur or perhaps simply was overlooked under these dramatic circumstances (14).

Recovery of vision has been reported in cobalt ocular toxicity after a decrease in ion concentration (15). Although cobalt levels dropped rapidly during the months after hip revision in our patient, her vision did not improve and optic atrophy developed. The patient’s course thus suggests that, as in other cases of toxic retinopathy or optic neuropathy, the effects may be irreversible when toxicity is severe and longstanding. However, improvement of her hearing, along with the recovery of her general health, is consistent with cobalt intoxication.

**CONCLUSIONS**

Through a chain of unfortunate circumstances, a mechanical orthopedic problem turned into a devastating visual loss in this case. Given the high prevalence of hip implants, every neuro-ophthalmologist should keep cobalt neurotoxicity in mind and ask patients with obscure visual loss about hip replacements. If cobalt intoxication is suspected, measurements of cobalt concentration should be prompted.

**ACKNOWLEDGMENTS**

The authors thank the patient for her cooperation and acknowledge the help of all the many physicians involved in treating the patient. The authors thank Dr Kathleen Digre for her helpful comments and Patrick Hofmann for providing part of the image material.

**REFERENCES**


FIG. 6. Myocardial biopsy performed 2 years after left hip revision. A. There is myocyte degeneration and atrophy (arrows) and necrotic myocytes with vacuolation of the cytoplasm (asterisks) consistent with cardiomyopathy (hematoxylin & eosin). B. Myocardial fibrosis (arrows) is also present (elastica van Gieson). Additional stainings showed no signs of storage disease or amyloidosis (not shown). The findings are not specific but consistent with cobalt cardiotoxicity.
Point Counter-Point

Section Editors: Andrew G. Lee, MD
Gregory Van Stavern, MD

Should Plasma Exchange Be Offered to Patients With Multiple Sclerosis–Associated Optic Neuritis?

John H. Pula, MD, Christopher C. Glisson, DO, MS

Isolated demyelinating optic neuritis (ON) is a relatively common cause of acute visual loss in adults and may be the presenting feature of both multiple sclerosis (MS) and neuromyelitis optica (NMO). Although most patients with MS-related ON recover spontaneously, some patients have permanent visual loss in the affected eye. There is evidence that plasma exchange (PLEX) can improve visual function in NMO-related ON, which often has poor visual recovery, but it remains uncertain whether such treatment benefits patients with MS-related ON. Two experts discuss this topic.

Pro: Plasma Exchange Should Be Offered to Patients With MS-Related Optic Neuritis: John H. Pula, MD

Although the Optic Neuritis Treatment Trial (ONTT) remains a landmark study, much has changed since its results first were reported. Orbital magnetic resonance imaging (MRI), optical coherence tomography, and serological markers are all now routinely used to help to differentiate etiologies of ON. We have found that some diseases, which cause ON, such as NMO, require different management strategies than other etiologies like MS. Although high-dose steroids remain the primary treatment option, I believe that in certain cases (including both NMO and MS), PLEX also should be used to treat ON.

There are several reasons why it makes pathophysiologic sense to use PLEX in selected cases of ON (I am referring herein to ON patients who do not respond to steroids): 1) PLEX has shown benefit in other demyelinating and inflammatory diseases besides ON, 2) PLEX is relatively safe, and 3) there are few other treatment options for steroid-resistant ON. In addition, we must remember the past to understand the present. In the past, some cases of presumed MS-related ON were ultimately found to be caused by NMO. In retrospect, treating these patients with PLEX may have produced improvement.

The logic behind using PLEX in MS-associated ON is supported by neuroimmunologic principles. The technique of PLEX involves removing a patient’s blood and separating the plasma from blood cells and platelets. The cells are then combined with a replacement fluid and returned to the patient. After 5 exchanges, native immunoglobulins and complement drop to <20% of their initial serum level (1–3). ON due to an MS exacerbation is now known to be associated with a humoral response involving B cells (4), so targeting these effector cells and eliminating them with PLEX makes sense in controlling the immune response.

A major concern for using PLEX in ON is the lack of controlled studies showing that PLEX works better than steroids alone or even better than the natural history of the condition itself. However, this does not exclude PLEX from being used in selected cases. There is evidence that PLEX benefits some patients with demyelinating disease, including those with relapsing–remitting MS (RRMS). Keegan et al (5) reviewed a series of patients treated with PLEX (22 MS, 10 NMO, 10 acute disseminated encephalomyelitis). Of this group, 44.1% had marked improvement after treatment. Early treatment with PLEX was strongly associated with improvement, usually seen within the first month.

There are several reports of the use of PLEX for ON. Roesner et al (6) evaluated 23 patients with ON: 12 clinically isolated syndrome (CIS), 1 NMO, and 10 RRMS. All patients received two 3- to 5-day cycles of 1 g intravenous methylprednisolone (IVMP), 2 weeks apart. Patients were offered PLEX if vision did not improve beyond 20/200 within 6 weeks of ON onset. On final follow-up (range, 21–331 days), 48% of patients improved at least 30% on acuity testing. Although there was no control, it was also noted that there were no major adverse events with PLEX. Another study included 41 patients who underwent PLEX for various demyelinating symptoms, most commonly para-paresis, but also ON. Mean Expanded Disability Scale Score (EDSS) before PLEX was 7.0, and range of time to treat with PLEX was 6–90 days. In 39% of patients, PLEX showed a significant EDSS improvement (median, 12 days). Importantly, 63% responded by 6 months (7). Another report presented the outcomes of 21 patients with steroid-unresponsive demyelinating relapses (2 NMO), including...
17 with ON. Duration between onset and PLEX was 11–300 days. Data were available in 8 patients during follow-up, and all showed improvement (8). Ruprecht et al (9) described 10 patients with ON ranging from 20/50 to no light perception from RRMS/CIS, all treated with 2 courses of IVMP and/or intravenous immunoglobulin. Time from symptom onset of ON to PLEX was 11–73 days. Seven of 10 had improvement within a range of 70–774 days. A limitation of all the above reports is that none had a control group, so natural history cannot be ruled out as the reason for improvement.

In contrast, the benefits for using PLEX in NMO are more accepted. There is Class I evidence that PLEX benefits steroid-refractory myelitis (10), and potentially, ON in NMO should respond similarly. A controlled trial found this to be true. Thirty-six patients with ON from NMO or NMO spectrum disease (NMOSD) were treated with 2 g IVMP × 3–5 days, and 16 with IVMP plus 5 consecutive treatments of PLEX. Initial visual acuity (VA) in both groups averaged 20/400. Final VA in the steroid-only group was 20/400, and in the PLEX group was 20/50 (11).

Based on the reports above, early additional treatment with PLEX may benefit some cases of steroid-refractory ON. There are many questions: 1) what clinical features define “poor response” to steroids, 2) what duration of time after steroids must pass before diagnosing “lack of response,” and 3) how early must PLEX be given to be effective after onset of ON? This is where the expertise of the neuro-ophthalmologist and future trials like the ONTT will be invaluable. We need more data regarding markers and predictors of atypical response or poor recovery in ON.

Should we wait for more data, or consider treating some cases now? This is the main question regarding PLEX in ON. In favor of treating now, we should recognize that NMO will not be the only serological marker discovered in ON. Recently, the myelin oligodendrocyte glycoprotein antibody has been found in the serum of NMO-seronegative patients with severe ON (12). It may be that these myelin oligodendrocyte glycoprotein positive patients are more similar to NMO than to MS in terms of treatment and PLEX response. If we withhold PLEX to certain ON patients who may benefit only because we have not yet defined a distinctive serological marker, we may be missing an opportunity for recovery.

PLEX is beneficial in myriad neuroimmunologic disorders, including Guillain–Barre syndrome, chronic inflammatory demyelinating polyneuropathy, myasthenia gravis, Lambert–Eaton syndrome, IgG–IgA related paraproteinemic polyneuropathy, Sydenham chorea, and natalizumab-associated progressive multifocal leukoencephalopathy (13). For ON, in patients with poor baseline VA who are NMO-seropositive, there is evidence to treat with PLEX. In appropriate patients with ON who are NMO-seronegative and are not experiencing visual recovery spontaneously or responding to high-dose steroids, I believe early PLEX should also be considered as a treatment option.

**Point Counter-Point**

**Con: Plasma Exchange Should Not Be Offered to Patients With MS-Related Optic Neuritis: Christopher C. Glisson, DO, MS**

ON is a common initial presentation of MS and can be expected to occur at some point in 50% of patients with an established diagnosis of MS (14). There is a greater risk of developing MS for patients presenting with CIS, defined as a first episode of ON or 1 or more other localizing neurologic deficits in association with MRI findings supportive of demyelination (15). For patients in each of these categories, the mainstay of ON treatment involves high-dose steroids (intravenous or oral) often followed by an oral prednisone taper. This therapeutic approach has been consistently shown to resolve the pain associated with ON and speed recovery of vision (16); however, no benefit from this (or any other acute pharmacologic intervention for ON) has been shown regarding altering the course of MS or the long-term recovery of vision.

ON, even when it occurs in patients with an established diagnosis of MS, has an excellent prognosis for visual recovery (15,17). It has been established that even in the absence of any treatment, the majority of patients with MS-related ON experience a significant recovery of vision with 72% of affected eyes maintaining vision of 20/20 or better at 15 years follow-up (18). Developing a new treatment strategy for inflammatory ON is superfluous, unless said treatment strategy can be shown to positively influence the course of demyelinating disease.

Therapeutic PLEX involves removing a large volume of the patient’s plasma with the goal of eliminating pathologic antibodies, immune complexes, and cytokines. It is presumed that PLEX may provide its benefit through T-cell modulation, suppression of interleukin 2, and interferon γ production (19,20). This high-volume removal requires replacement fluid, typically human albumin, to mitigate hypovolemia and circulatory collapse during the procedure. In addition, PLEX requires venous access, typically through a central venous line; this is associated with discomfort for the patient and induces additional risks including bleeding, infection, and iatrogenic trauma to vulnerable organ systems (21).

There are reports of improved visual outcomes for patients with NMO-related ON through the use of PLEX as an adjunct to IVMP. In contrast to MS, NMO is an autoimmune inflammatory disease that is characterized by
antibodies against aquaporin-4 (22). Distinct from most cases of MS, the clinical manifestations of NMO commonly include bilateral, severe ON (often with poor visual recovery) and transverse myelitis with the potential for severe and unremitting neurologic disability. It has become increasingly accepted that the pathophysiology of NMO differs significantly from that of traditional MS, and it is clear that patients with NMO-related ON have a far worse prognosis (visual and otherwise) than their MS counterparts (23). This justifies the use of aggressive, and potentially disease-altering, therapies such as PLEX in this patient population.

At present, a similar case for the aggressive management of MS-related ON lacks support. Patients with NMO have poor visual recovery and more significant loss of retinal nerve fiber layer with each episode of ON (24,25); this effect is not commonly seen in MS-related ON. Additionally, NMO-related ON is characterized by bilateral optic nerve and chiasm involvement, as distinct from MS-related ON (26). Based on these observations, the use of PLEX in MS-related ON cannot be justified particularly when there is inexpensive, reasonably convenient, and safe alternative. Another important aspect to consider in our changing healthcare landscape is the significant expense of PLEX: the fee-for-service portion of the procedure alone may exceed US $5,500, and this does not include the cost of central venous access, albumin, and any ancillary medications required for the procedure. In my opinion, PLEX should be reserved for patients with severe conditions for which evidence has shown its efficacy, including ABO-incompatible solid organ and stem cell transplant, acute inflammatory demyelinating polyradiculoneuropathy (Guillain–Barré syndrome), severe vasculitis, Wegener granulomatosis, and polyneuropathies related to paraprotein disorders.

Rebuttal: John H. Pula, MD

Dr. Glisson has properly explained why PLEX is not considered a standard treatment for typical MS-related ON. I agree with many of his points, including that, in general, most patients with ON should not be treated with PLEX. I also agree that, in some cases, NMO-related ON can be distinguished from MS and treated accordingly. I would argue that there are instances of idiopathic or MS-related ON, which require an escalated level of treatment. As mentioned by Dr. Glisson, no large-scale clinical trials exist to guide the physician in these cases, so we are limited to smaller series and individual reports to make our decisions. I submit that the use of PLEX has generated the greatest amount of evidence as a treatment of steroid-refractory ON. I also agree with Dr. Glisson that the cost of PLEX is substantial; however, the potential costs of disability, lost work, and low vision programs from unrecovered vision loss would quickly outweigh this cost. I would disagree with Dr. Glisson that the risks of PLEX, when clinically warranted, outweigh its potential benefits. In fact, corticosteroids, which have no effect on extent of vision recovery, can result in pancreatitis, acute psychosis, and myriad other adverse effects, yet we regard their use as first line treatment for ON. In conclusion, PLEX should be considered in certain cases of ON, which are not responsive to steroids and require further treatment. It is to be expected that until we have more data, there will be some level of treatment variance in ON, but I believe that PLEX is an option which should be considered.

Rebuttal: Christopher C. Glisson, DO, MS

Dr. Pula provides several compelling statements in support of the use of PLEX for the treatment of ON. Much has been learned since the ONTT concerning the natural history of ON, as well as the myriad emerging atypical (or “non-MS related”) varieties of ON. However, the greatest challenge for the clinician is accurately identifying an “atypical” presentation that should warrant consideration of PLEX and providing counsel to patients regarding their anticipated outcome in the face of limited evidence-based data.

There is an accumulating body of evidence to support the efficacy of PLEX for patients with an established diagnosis of NMO. No objection can be made to the assertion that the currently understood pathophysiologic mechanism of inflammation in NMO and NMOSD lends itself to the utilization of a treatment such as PLEX.

However, as Dr. Pula notes, there have been no controlled trials to definitively establish that the use of PLEX offers a better outcome than intravenous steroids (or natural history alone), in patients with MS-related ON. Consideration of PLEX for patients with (presumably MS-related) ON that does not respond to established treatment paradigms in typical fashion is an intriguing suggestion. Although exact criteria for this scenario have not been clearly defined and, as such, it falls to the clinician to evaluate this on a case-by-case basis. As reported in the study cited by Dr. Pula, only 50% of such patients treated with PLEX improved by a minimal 30%; this was documented over a range of 21–331 days, which does not eliminate the possibility of some improvement on the basis of natural history alone.
In summary, I am in agreement with Dr. Pula that PLEX is a logical consideration for patients with ON in the setting of a clearly established diagnosis of NMO or other aggressive demyelinating process for which the utilization of PLEX is pathophysiologically reasonable. However, the present time, identifying these patients (particularly early in their course) can be challenging. For patients with typical MS-related ON, treatment with corticosteroids following the ONTT protocol remains safe, effective, and inexpensive, with a well-established clinical outcome. Steroid treatment for MS-related ON is clearly preferable to the utilization of an expensive, inconvenient, and superfluous treatment such as PLEX.

CONCLUSIONS

As with many neuro-ophtalmic disorders, there is no high quality evidence guiding the management of the patient with severe MS-related ON and poor visual recovery. PLEX remains an intriguing alternative for such patients, but questions remain regarding the identification of the appropriate patient population and the timing of initiating treatment. A high index of suspicion for seronegative NMO (e.g., normal or atypical MRI, bilateral involvement) is one scenario in which early institution of PLEX might be considered. As the authors’ note, the decision must be made on a case-by-case basis.

REFERENCES


Literature Commentary


Introduction: Nonarteritic anterior ischemic optic neuropathy (NAION), a rare visual disorder, has been reported in men using phosphodiesterase type 5 inhibitors (PDE5i) for erectile dysfunction.

Aim: We examined whether intermittent use of PDE5i is associated with acute NAION onset within approximately 5 half-lives after drug ingestion.

Methods: One hundred two ophthalmology centers in the United States and Europe identified potential cases of NAION. An expert adjudication committee conducted a blind review of the records of those with recent PDE5i use to classify cases as Definite, Possible, or not NAION. Subjects provided information on PDE5i use through telephone interview. Each NAION case’s PDE5i exposure immediately before onset was compared against his recent patterns of use in an observational case-crossover design. A sample size of 40 cases with intermittent PDE5i exposure in the 30 days before NAION onset was needed to detect an odds ratio (OR) of 3.0 with 80% power.

Main Outcome Measures: The daily relative risk for acute NAION on days within 5 half-lives of PDE5i use vs other days was estimated through an OR obtained from conditional logistic regression.

Results: Among 43 Definite NAION cases with PDE5i exposure in the prior 30 days, the OR was 2.15 (95% confidence interval [CI]: 1.06–4.34). When 21 Possible NAION cases were included (n = 64), the OR was 2.36 (95% CI: 1.33–4.19).

Conclusions: We found an approximately 2-fold increased risk of acute NAION within 5 half-lives of PDE5i use compared with use in a more prior time period. Bias from inaccurate recall of exposure was unlikely to have substantially affected the results. Based on our results, we estimate that weekly use of PDE5i adds 3 NAION cases per 100,000 men of 50 years and older annually.

In this study, men with nonarteritic anterior ischemic optic neuropathy (NAION) were asked about their use of phosphodiesterase type 5 inhibitor (PDE5i). Subjects indicated PDE5i use 1 day before the onset of visual symptoms (case) vs 2–30 days before (control). The study also looked at whether there was a difference in PDE5i use in the week before symptom onset vs 2–8 weeks prior. The risk of NAION after PDE5i use in both analyses was increased by more than 100%.

Finally, we have a prospective rigorous study that clearly associates PDE5i use with NAION. We should ask all men with NAION about PDE5i use. In the European Union, PDE5i use is not recommended for patients with a history of NAION. If we assume that PDE5i use doubles the risk of fellow eye involvement, which is already around 15%–25%, then all clinicians should really consider recommending the same for patients with unilateral NAION.

—Michael S. Lee, MD

This case-crossover design trial came up with 2 different estimates of the number of additional cases of NAION expected from PDE5i use. Estimating a use of 1 in 5 days yields a risk of an additional 3 annual cases of definite NAION per 100,000 patients. However, daily use yields a risk of an additional 34 annual probable or definite cases of NAION per 100,000 patients. This study adds to a controversial literature with claims on the one hand that NAION is caused by PDE5i, but others claiming that NAION is caused by the same risk factors causing erectile dysfunction (ED).

Michael, let’s not get ahead of ourselves and claim as you have that, “Finally, we have a prospective rigorous study that clearly associates PDE5i use with NAION.” I’d ask you to consider the study below published ahead of print in the Journal of Neuro-ophthalmology (JNO) by Nathoo et al (1). That case-control study did not find an increased risk of NAION in patients “prescribed” ED drugs. Of course, there are limitations in the study (e.g., there was no information in this healthcare database on whether some patients may have obtained ED drugs not officially prescribed).

So, although there is evidence implicating PDE5i in NAION, the controversy continues!! Stay tuned for the JNO session on this topic at NANOS 2015 in San Diego!

—Mark L. Moster, MD

Thanks for bringing the Nathoo et al article up. This was a retrospective review of claims data. The cases and controls were significantly different; there was no expert who diagnosed NAION, and use of PDE5i was inferred because prescriptions were filled. They concluded that no association exists between filling a prescription for PDE5i and receiving a diagnostic code for NAION. Mark, the
Nathoo et al article is not prospective, rigorous, or convincing. I stand by my statement.

—Michael S. Lee, MD

REFERENCE


Importance: Hydroxychloroquine sulfate retinopathy can progress after the drug is stopped. It is not clear how this relates to the stage of retinopathy or whether early screening with modern imaging technology can prevent progression and visual loss.

Objective: To determine the relationship between progression of retinopathy and the severity of disease using objective data from optical coherence tomography and assess the value of early screening for the toxic effects of hydroxychloroquine.

Design, Setting, and Participants: Clinical findings in patients with hydroxychloroquine retinopathy were monitored with repeated anatomical and functional examinations for 13–40 months after the drug was stopped in a referral practice in a university medical center. Eleven patients participated, with the severity of toxic effects categorized as early (patchy parafoveal damage shown on field or objective testing), moderate (a 50%–100% parafoveal ring of optical coherence tomography thinning but intact retinal pigment epithelium), and severe (visible bull's-eye damage).

Main Outcomes and Measures: Visual acuity, white 10-2 visual field pattern density plots, fundus autofluorescence, spectral density optical coherence tomography cross sections, thickness (from cube diagrams), and ellipsoid zone length.

Results: Visual acuity and visual fields showed no consistent change. Fundus autofluorescence showed little or no change except in severe cases in which the bull's-eye damage expanded progressively. Optical coherence tomography cross sections showed little visible change in early and moderate cases but progressive foveal thinning (approximately 7 µm/y) and loss of ellipsoid zone (in the range of 100 µm/y) in severe cases, which was confirmed by quantitative measurements. The measurements also showed some foveal thinning (approximately 4 µm/y) and deepening of parafoveal loss in moderate cases, but the breadth of the ellipsoid zone remained constant in both early and moderate cases. A few cases showed a suggestion of ellipsoid zone improvement.

Conclusions and Relevance: Patients with hydroxychloroquine retinopathy involving the retinal pigment epithelium demonstrated progressive damage on optical coherence tomography for at least 3 years after the drug was discontinued, including loss of foveal thickness and cone structure. Cases recognized before retinal pigment epithelium damage retained foveal architecture with little retinal thinning. Early recognition of hydroxychloroquine toxic effects before any fundus changes are visible, using visual fields and optical coherence tomography (along with fundus autofluorescence and multifocal electroretinography as indicated), will greatly minimize late progression and the risk of visual loss.

Intuitively, finding hydroxychloroquine toxicity earlier leads to less visual loss. This study verifies that by optical coherence tomography (OCT) measurements of foveal thickness and loss of ellipsoid zone, those who discontinue the medication with early toxicity remain stable, while those with severe involvement continue to have progressive deterioration for the next 3 years. Although the study is very small and follow-up only 2 to slightly more than 3 years, it emphasizes the need for appropriate monitoring of patients for early diagnosis and discontinuation of the medication.

—Mark L. Moster, MD

The fundus autofluorescence and OCT progression are striking for the severe cases of toxicity, and I’m interested to see if longer follow-up will show further progression. Fortunately, the visual acuity and visual fields did not progressively worsen in any of the patients for the first 3 years of follow-up, and I think we can reassure patients with toxicity about the functional data.

—Michael S. Lee, MD


Purpose: We investigated longitudinal changes in retinal nerve fiber layer (RNFL) thickness after vitrectomy for epiretinal membrane (ERM).

Methods: Thirty-one patients who underwent pars plana vitrectomy with internal limiting membrane peeling for ERM were included. Average thickness and 4 quadrants of RNFL thickness were determined before and at 1, 3, 6, and 12 months after surgery by spectral domain optical coherence tomography. As macular lesions could affect RNFL thickness, we evaluated changes in RNFL thickness by dividing the RNFL into 12 o'clock hourly positions, defining pathologic area adjacent to the lesion and nonpathologic area.

Results: RNFL thickness of the affected eyes increased at 1 month after vitrectomy and later decreased compared with baseline values. Temporal quadrant RNFL thickness was statistically significantly thicker in affected eyes at baseline and at 1 month after surgery and thinner after 12 months than fellow eyes. RNFL thickness in pathologic area decreased after surgery, and the RNFL was statistically significantly thinner at 3, 6, and 12 months postoperatively, compared with the baseline thickness. The RNFL thickness of pathologic area of affected eyes compared with fellow eyes was thicker both at baseline and 1 month after surgery but thinner at 12 months compared with baseline values.

Conclusions: Postoperative RNFL thickness after vitrectomy combined with ERM removal tended to decrease postoperatively. RNFL thicknesses in temporal pathologic area were significantly reduced at 3, 6, and 12 months postoperatively.

Purpose: Macular pucker (MP) and macular hole (MH) are vitreomacularopathies treated by vitrectomy and membrane peel. The complication of postoperative central scotoma can be associated with significant reduction in visual acuity (VA). We seek to determine whether retinal nerve fiber layer (RNFL) disruption is the pathophysiologic basis of this defect. Mitigating clinical circumstances also were sought.

Methods: Eleven eyes from 10 pseudophakic patients who had undergone vitrectomy with peeling for either MH or MP were studied with clinical measures, including optical coherence tomography (OCT). Membrane specimens were evaluated by immunohistochemistry for neurofilament, a marker for the inner retina. Ten eyes from 10 pseudophakic patients who underwent repeat surgery for persistent or recurrent pathology were evaluated to determine the relationship between the timing of reoperation and clinical outcome.

Results: Cases with a postoperative central scotoma (N = 4) had worse VA (~20/600) compared with those without (N = 7, ~20/30, P = 0.01). Eyes with a central scotoma had significantly reduced RNFL thickness in the temporal quadrant (53.67 vs 72.33 μm, P = 0.05) by OCT. A central scotoma was associated with more disruption of the inner retina on immunohistochemistry (P = 0.03). In patients with persistent or recurrent pathology, waiting 6 months before reoperation resulted in better functional outcomes (P = 0.03).

Conclusions: Central scotomata and poor VA were associated with disruption of the RNFL during membrane peeling. Affected patients have RNFL thinning and signs of optic neuropathy, for which we propose the term inner retinal optic neuropathy (IRON). In patients requiring reoperation, waiting 6 months between surgeries may reduce the risk of IRON.

It has long been observed that patients can have what looks like an optic neuropathy after vitrectomy. Both of the abstracts above address this issue.

In the second study, Pan et al retrospectively looked at various vitrectomies including ERM peeling alone, ILM peeling, and air-fluid exchange for macular hole repair. They compared the visual function and RNFL of eyes that experienced a good visual outcome vs a poor visual outcome and found that eyes with the latter had significantly thinner RNFL. They looked at the timing of repeat vitrectomy and found that repeat surgery <6 months experienced worse visual outcomes and thinner RNFL compared with eyes with repeat surgery >6 months. This study did not compare the RNFL thickness with baseline values or normal eyes. The authors also performed immunohistochemistry on the peeled membranes for the presence of neurofilament and found that eyes with the worst visual acuities were more likely to stain positively. This suggests that the RNFL itself was peeled along with the ERM or ILM during the surgery.

From the results of both studies, it appears that the RNFL commonly becomes significantly thinner after all vitrectomies. Eyes with poorer visual outcomes experience substantially more thinning of the RNFL. If an eye needs repeat vitrectomy and ERM peeling, then it may be reasonable to wait 6 months.

—Michael S. Lee, MD


Abstract: The objective of residency training is to produce physicians who can function independently within their chosen subspecialty and practice environment. Skills in the business of medicine, such as clinical billing, are widely applicable in academic and private practices but are not commonly addressed during formal medical education. Residency and fellowship training include limited exposure to medical billing, but our academic department’s performance of these skills was inadequate; in 56% of trainee-generated outpatient notes, documentation was insufficient to sustain the chosen billing level. We developed a curriculum to improve the accuracy of documentation and coding and introduced practice changes to
address our largest sources of error. In parallel, we developed tools that increased the speed and efficiency of documentation. Over 15 months, we progressively eliminated note devaluation, increased the mean level billed by trainees to nearly match that of attending physicians, and increased outpatient revenue by $34,313 per trainee per year. Our experience suggests that inclusion of billing education topics into the formal medical curriculum benefits both academic medical centers and trainees.

In response to billing audits, which found errors in 56% of patient encounters in resident’s clinic, the Division of Pediatric Neurology at Boston Children’s Hospital embarked on a program to train the residents in proper documentation. This included 4 hours of lectures and individualized structured feedback for each resident. Initial errors included in declining order: inadequate review of systems, insufficient documentation to justify billing as a new patient, medical decision making, physical exam, undercoding, overcoding, medical history. After the training, accuracy improved from 44%, sustaining the audit to 93%. Financially, this resulted in an increase in revenue of $34,313 per trainee per year.

In addition to the obvious financial benefit to academic departments and medical centers, this type of training will certainly help the transition from training to practice.

As the accompanying editorial by Kaminski and Busis emphasized, we best educate residents in the “3 legs that support and health care delivery platform: the art, science and business of medicine.”

—Mark L. Moster, MD

I know that I did not receive any type of billing education in residency, and I had a rude awakening in fellowship and my first job. Our current ophthalmology residents have access to coding courses annually, but very few take advantage of it. Making coding a part of an already crowded curriculum would have great overall value to help the graduate hit the ground running. I think the financial incentive to the departments only applies to those where the residents fill out their own billing. I think it is also harder to make the coding information stick when residents are not part of the billing process.

—Michael S. Lee, MD


**Importance:** Patients with neuromyelitis optica who have aquaporin-4 antibodies are being identified and receiving immunosuppressant treatment earlier and more aggressively as a result of increasing awareness of the importance of preventing relapses responsible for the high morbidity and mortality associated with the disease. To our knowledge, opportunistic retinal infection in patients with aquaporin-4 antibodies who are receiving immunosuppressants has not been reported to date.

**Observations:** We describe 2 patients with aquaporin-4 antibodies who were receiving conventional doses of first-line immunosuppressive therapy. Both patients presented with vision loss that was initially thought to be optic neuritis attacks. The subsequent diagnoses were ocular toxoplasmosis and cytomegalovirus retinitis.

**Conclusions and Relevance:** Retinal opportunistic infections can occur in patients with aquaporin-4 antibodies who are receiving relatively low levels of immunosuppression, may mimic optic neuritis, and are a potentially reversible cause of vision loss when treated promptly.

The default diagnosis in a patient with visual loss who has aquaporin-4 antibodies and either classic neuromyelitis optica or a variant would be an episode of optic neuritis. However, this article describes one case of cytomegalovirus retinitis and one of ocular toxoplasmosis and highlights to me the importance of a thorough ophthalmic examination in anyone with visual loss. This is reminiscent of the patient with multiple sclerosis who is on natalizumab and who has what mimics an exacerbation, but really has progressive multifocal leukoencephalopathy. Of course, the treatments in both these situations are dramatically different. On the one hand, an exacerbation of neuromyelitis optica or multiple sclerosis may require treatment with steroids and boosting up the immunosuppression. On the other hand, an infection with progressive multifocal leukoencephalopathy or infectious retinitis must be treated with anti-infectious agents and not increasing the immunosuppression.

We must emphasize to our neurology colleagues that anyone with visual loss needs a thorough funduscopic examination. We’ve likely all had cases called central retinal artery occlusion that were retinal detachments or optic neuritis that were central serous retinopathy.

—Mark L. Moster, MD

I have seen the patient with NMO, treated by the neurologist for presumed optic neuritis. When she did not get better, she was sent for evaluation to find out that she had a retinal detachment. Although statistically vision loss is more apt to be optic neuritis, Hickam’s dictum can always rear its head.

I think the clinician could also get a good orbital magnetic resonance imaging with fat suppression and gadolinium. The absence of T2 hyperintensity or gadolinium enhancement should prompt him/her to seek an ophthalmic consultation because it may not represent optic neuritis.

—Michael S. Lee, MD
Renal Cell Carcinoma Metastatic to the Orbit in a Patient With Wegener Granulomatosis

We read with great interest the editorial “Tigers and Snakes in Neuro-Ophthalmology,” which discussed, among other things, Occam razor and Hickam dictum (1). We evaluated a patient with long-standing Wegener granulomatosis, untreated during the preceding 6 months, who presented with proptosis, diplopia, and compressive optic neuropathy from a renal cell carcinoma (RCC) metastasis to the orbit, supporting Hickam dictum that “Patients can have as many diseases as they damn well please.”

A 71-year-old man reported vision loss in both eyes and horizontal binocular diplopia for several weeks. In addition, he noted mild left eye pain and occasional epistaxis. He had been diagnosed with Wegener granulomatosis 13 years before on the basis of a renal biopsy. The disease was limited to his kidneys and had been well controlled with various combinations of cyclophosphamide, azathioprine, and prednisone. His recent treatment had included oral prednisone (7.5 mg daily) and azathioprine (150 mg daily). However, against medical advice, he had stopped taking his immunosuppressants for 6 months before presentation. His history was remarkable for Graves’ disease with lid retraction (but no other symptoms or signs to suggest thyroid eye disease), atrial fibrillation, hypertension, diabetes mellitus, and a subdural hematoma requiring surgical evacuation.

On examination, vision was 20/50, right eye and 20/200, left eye. Pupils were isocoric, but there was left relative afferent pupillary defect of 1.5 log units. There was 3 mm of proptosis of the left eye with a moderate left abduction deficit. Anterior segment examination revealed bilateral cataracts, and intraocular pressures were normal. Dilated funduscopic examination showed trace temporal optic disc pallor in the left eye. Kinetic visual fields revealed central depression in the right eye and a dense cecocentral scotoma in the left eye.

Magnetic resonance imaging (MRI) showed a well-circumscribed extraconal mass in the lateral portion of the left orbit (Fig. 1A, B). On computed tomography (CT), the mass was noncalcified, extending into the superior orbital fissure, and eroding the greater wing of the sphenoid base (Fig. 1C). There was no sinus disease on MRI or CT.

Laboratory investigations revealed positive P-ANCA (titer, 1:2560) and myeloperoxidase antibodies (titer >8.0). Proteinase 3 antibodies were not detected. The elevated P-ANCA titer suggested a possible Wegener granulomatosis relapse. Because there was a compressive left optic neuropathy and the imaging findings were atypical for orbital involvement from Wegener granulomatosis, a lateral orbitotomy was performed.

Histologically, the lesion consisted of lobules of cells separated by a fine capillary network (Fig. 2). The cells had round-to-oval-shaped nuclei and abundant clear cytoplasm, some with foamy cytoplasmic vacuoles. The nuclei ranged from bland to moderately pleomorphic with nuclear vacuoles and prominent nucleoli. Immunohistochemistry (IHC) demonstrated positivity with pancytokeratin, AE1/AE3, PAX8, and vimentin with focal positivity with the RCC marker. IHC for cytokeratins 7 and 20 were negative. These findings were consistent with the clear cell variant of RCC. CT of the chest, abdomen, and pelvis showed an 11·15·11 cm right renal mass, compatible with RCC, with multiple pulmonary nodules and a lytic lesion in the right femur suspicious for metastases.

The patient was treated with radiation therapy to the femoral lesion and pazopanib (selective tyrosine kinase inhibitor) chemotherapy.

Although a metastatic lesion to the left orbit was considered in the differential diagnosis of our patient, the finding of a RCC metastasis was unexpected. This neoplasm accounts for approximately 5% of orbital metastases (2).
Although rare, there are reports of Wegener granulomatosis associated with RCC. The 2 entities may present simultaneously (3), or RCC may develop years after diagnosis of Wegener granulomatosis (4–6). Simultaneous presentation of these conditions has led some to speculate that the 2 diseases share a collective pathogenetic pathway and that the malignancy may even contribute to the development of autoimmunity and vasculitis (3). In contrast, the delayed presentation of RCC suggests that immunosuppressive treatment, especially cyclophosphamide, may be responsible for the increased risk of RCC (4–6). Cyclophosphamide has been implicated in the development of other malignancies, including bladder cancer and acute myeloid leukemia, especially if the cumulative dose exceeds 36 g (7). Because our patient presented with RCC 13 years after the diagnosis of Wegener granulomatosis, we believe that immunosuppressive therapy likely contributed to the development of the malignancy.

John J. Chen  
Department of Ophthalmology and Visual Sciences,  
University of Iowa, Iowa City, Iowa

Namrata Singh  
Department of Rheumatology, University of Iowa,  
Iowa City, Iowa

John J. Brinkley  
Amanda C. Maltry  
Department of Ophthalmology and Visual Sciences,  
University of Iowa, Iowa City, Iowa

Bruno A. Policeni  
Department of Radiology, University of Iowa,  
Iowa City, Iowa

Nasreen A. Syed  
Department of Ophthalmology and Visual Sciences,  
University of Iowa; Department of Pathology,  
University of Iowa; and Ophthalmology Service,  
Iowa City VA Medical Center, Iowa City, Iowa

Richard C. Allen  
Department of Ophthalmology and Visual Sciences,  
University of Iowa; Department of Otolaryngology—Head and  
Neck Surgery, University of Iowa, Iowa City, Iowa

Reid A. Longmuir  
Department of Ophthalmology and Visual Sciences,  
University of Iowa; Ophthalmology Service,  
Iowa City VA Medical Center, Iowa City, Iowa
Progressive MRI Findings in Creutzfeldt–Jakob Disease

Parkinson et al (1) recently reported characteristic magnetic resonance imaging (MRI) findings in 2 confirmed cases of the Heidenhain variant of Creutzfeldt–Jakob disease. The following is a similar case that demonstrates progressive neuroimaging abnormalities.

An 89-year-old woman complained of dizziness, unsteadiness, disruption of her sleep pattern, forgetfulness, and gradually worsening vision for several months. She had fallen many times and recently stopped driving. She denied fever, headaches, or other focal neurologic symptoms. She underwent a neurologic examination, which was reported as unremarkable, and MRI was reported to be normal except for age-related atrophy. Her symptoms were attributed to Alzheimer disease. Her dizziness was treated with meclizine with no relief.

FIG. 1. A. Diffusion-weighted imaging shows subtle ribbon-like areas of restricted diffusion along the gyri of the right cerebral hemisphere. B. Repeat imaging 1 month later demonstrates progression of the disease and involvement of the left occipital cortex.
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FIG. 1. A. Diffusion-weighted imaging shows subtle ribbon-like areas of restricted diffusion along the gyri of the right cerebral hemisphere. B. Repeat imaging 1 month later demonstrates progression of the disease and involvement of the left occipital cortex.
One month later, the patient experienced a rapid decline with difficulty ambulating and performing activities of daily living. Her family noted emotional outbursts, startle myoclonus, and left-sided neglect. On neuro-ophthalmologic testing, she was oriented to person and place only. Visual acuity was counting fingers in both eyes. She could not read the Ishihara color plates and had spasm of fixation. Confrontation visual fields suggested bilateral homonymous hemianopias, denser on the left than the right. Pupils reacted normally to light. Ocular examination was otherwise unremarkable. She had mild rigidity of both upper extremities and increased deep tendon reflexes.

Repeat brain MRI (Fig. 1B) showed ribbon-like areas of restricted diffusion along the gyri of the right cerebral hemisphere and left occipital lobe on diffusion-weighted imaging (DWI). In retrospect, these areas were visible, but more subtle, on the initial MRI (Fig. 1A).

Cerebrospinal fluid (CSF) studies revealed a positive 14-3-3 protein and positive t of 3872 pg/mL, as well as a positive real-time quaking-induced conversion assay (2). The remainder of the CSF studies were normal. A 16-channel electroencephalogram showed periodic frontally dominant sharp wave discharges with periodicity of 1–2 Hz in the right hemisphere. The patient was discharged to hospice and died 2 weeks later.

An autopsy specimen of the brain was sent to the National Prion Research Center at Case Western Reserve University in Cleveland, OH. Immunohistochemical analysis on the autopsy tissue with 3F4, the monoclonal antibody to the prion protein (PrP), revealed granular deposits typical of prion disease (Fig. 2). Western blot analysis revealed the presence of abnormal protease resistant PrP without a pathogenic mutation in the coding region of the PrP gene. Further historical information from the family revealed that the patient had exposure to raw undercooked meat in Germany in the 1980s, and she had lived with a friend at that time who died of “mad cow disease.”

Unlike other causes of dementia, prion disease may be associated with high signal in the basal ganglia, thalamus, or along the cortical ribbon on DWI, fluid-attenuated inversion recovery, or T2-weighted MRI sequences, with a sensitivity and specificity of >90% (3–5). However, these subtle changes are often missed. The cause for restricted diffusion is attributed to abnormal vacuoles in the cytoplasm and microvacuolation of neurons leading to spongiform degeneration, cell lysis, and membrane disruption. We emphasize the importance of these neuroimaging findings, as they can aid in early and accurate diagnosis of this rapidly progressive and fatal condition.

Kaushal M. Kulkarni, MD
Department of Ophthalmology, Sharp Rees-Stealy Medical Group, San Diego, California

The author reports no conflicts of interest.
Autoimmune Acquired Rippling Muscle Disease and Myasthenia Gravis

We present an intriguing postscript to a case published by Kosmorsky et al (1) in this journal in 1995. It concerned a 58-year-old man with intermittent diplopia, arm, and leg weakness, dysarthria, and muscle rippling. Examination demonstrated intermittent esotropia triggered by prolonged convergence. Creatine phosphokinase (CPK) was mildly elevated at 676 IU (normal range 293–378 IU). Electromyography (EMG) showed electrically silent percussion-induced muscle rippling. Muscle biopsy showed a nonspecific myopathy consisting of rare interstitial and perivascular lymphocytic infiltrates, scattered atrophic type I and II muscle fibers, and electron microscopic subsarcolemmal honeycomb structures. The authors interpreted these findings as consistent with rippling muscle disease (RMD). The patient was treated with calcium channel blocking agents without response.

The same patient was reported the next year by Ansevin and Agamanolis (2), who had examined him 16 months before and 3 years after he was examined by Kosmorsky. The patient’s first visit had been prompted by painful muscle rippling and cramping. Examination disclosed percussion-induced muscle rippling and mild proximal extremity weakness. EMG did not reveal myotonia. CPK was elevated. At the patient’s second visit 5 years later, the muscle rippling had mostly resolved, his principal complaints now being bilateral ptosis, diplopia, dysphagia, and weakness. Examination revealed fatigable neck and proximal extremity weakness. Rest and edrophonium tests suggested myasthenia gravis (MG). EMG showed a decremental response on repetitive stimulation without improvement with exercise and no myotonia. Acetylcholine receptor antibody was elevated at 64 nmol/L (normal <0.02 nmol/L), and skeletal muscle antibody titer was elevated at 1:320 (normal <1:60). Chest computed tomography revealed a thymic mass, and muscle biopsy showed a nonspecific myopathy, exactly as described by Kosmorsky. Ansevin and Agamanolis did not diagnose RMD but rather MG with muscle rippling. Thymectomy and treatment with pyridostigmine and plasmapheresis improved the clinical manifestations.

Therefore, the same patient evaluated by 2 physicians at different times with similar EMG, and muscle biopsy findings was assigned completely different diagnoses. Which diagnosis is correct? We encountered a similar patient recently who led us to believe that both diagnoses are probably correct.

Our patient was a 52-year-old former Olympic-level athlete who presented with cramping and stiffness of arms, legs, and chest for 4 years without weakness. He had been examined extensively by rheumatologists, the only abnormal laboratory test being a mildly elevated CPK. Our examination disclosed percussion-induced muscle rippling of the chest, arms, and thighs (See Supplemental Digital Content, Video 1, http://links.lww.com/WNO/A116). A paraneoplastic panel revealed an elevated striated muscle antibody titer of 1:61,440 (normal <1:60) and an elevated acetylcholine receptor binding antibody at 4.35 nmol/L (normal <0.02 nmol/L). EMG showed non-electrically silent muscle rippling without myotonia. There was no decrement on repetitive stimulation or clinical evidence of MG. We diagnosed RMD.

Five months later, he developed binocular diplopia. Examination disclosed an exodeviation on right gaze, fatigable right upper lid ptosis, persistent muscle rippling, but no extremity or bulbar weakness (See Supplemental Digital Content, Video 2, http://links.lww.com/WNO/A117). CAV3 testing was negative. Now, we diagnosed a combination of RMD and MG. Treatment with pyridostigmine was unhelpful, but ptosis, diplopia, and muscle rippling resolved after several weeks’ treatment with mycophenolate 2000 mg/d and prednisone 20 mg/d.

There are now 14 reported cases of concurrent RMD and MG (1–7). The classic form of RMD is an autosomal dominant caveolinopathy associated with a CAV3 mutation (8). Other CAV3-related caveolinopathies include limb girdle muscular dystrophy-1C, distal myopathy, idiopathic creatine phosphokinase elevation, and familial hypertrophic cardiomyopathy (9). In the acquired autoimmune form, there is no family history of RMD, and CAV3 testing is negative. Clinical manifestations develop after the second decade of life, later than in hereditary RMD (10). Muscle rippling may not be electrically silent on EMG (5). Muscle biopsy discloses nonspecific myopathic findings and rare areas of inflammation (7), abnormalities that are not found in hereditary RMD or in MG.
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The clinical importance of recognizing concurrent RMD and MG is that muscle rippling in this condition improves after immunosuppression (6,7) but worsens after treatment with conventional doses of acetylcholinesterase inhibitors, which likely unmask the muscle hyperexcitability of RMD. As in patients with MG and thymoma, antibodies are directed at the muscle protein titin but at a different site. This case also further highlights the very low true false-positive rate of acetylcholine receptor antibodies (0.05%) (1), such that even in the absence of clinical symptoms or electrophysiologic findings, the presence of these antibodies may anticipate the later development of MG.

Dane A. Breker, MD
Department of Ophthalmology and Visual Sciences
University of Michigan
Ann Arbor, MI

Ann A. Little, MD
Department of Neurology
University of Michigan
Ann Arbor, MI

Jonathan D. Trobe, MD
Department of Ophthalmology and Visual Sciences
University of Michigan
Ann Arbor, MI

The authors report no conflicts of interest.

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Bitemporal Hemianopia Secondary to Nasal Staphylomata

The interesting article by Wang et al (1) seeks to explain the mechanism of bitemporal hemianopia due to chiasmal compression. Our case is a reminder that bitemporal hemianopia may be secondary to refractive optical effects and mechanical effects on the optic chiasm. A 68-year-old woman with an 18-month history of a generalized headache was noted to have a bitemporal visual field defect by her optometrist and was referred for further evaluation.

FIG. 1. Both optic discs are tilted with less pigmentation of the nasal retina bilaterally.
The clinical importance of recognizing concurrent RMD and MG is that muscle rippling in this condition improves after immunosuppression (6,7) but worsens after treatment with conventional doses of acetylcholinesterase inhibitors, which likely unmask the muscle hyperexcitability of RMD. As in patients with MG and thymoma, antibodies are directed at the muscle protein titin but at a different site. This case also further highlights the very low true false-positive rate of acetylcholine receptor antibodies (0.05%) (1), such that even in the absence of clinical symptoms or electrophysiologic findings, the presence of these antibodies may anticipate the later development of MG.

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University of Michigan  
Ann Arbor, MI

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Department of Neurology  
University of Michigan  
Ann Arbor, MI

Jonathan D. Trobe, MD  
Department of Ophthalmology and Visual Sciences  
University of Michigan  
Ann Arbor, MI

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FIG. 1. Both optic discs are tilted with less pigmentation of the nasal retina bilaterally.
urgently to the Ophthalmology Department. Her visual acuities were 20/30 in each eye when corrected for myopia and astigmatism (right eye: $-6.25 + 2.00 \times 77$; left eye: $-5.75 + 1.50 \times 97$). Intraocular pressures were normal in each eye. Ophthalmoscopy showed tilted optic discs with peripapillary atrophy but healthy neuroretinal rims and pale nasal retinas bilaterally (Fig. 1). Automated visual field testing (24-2) with the patient’s reading prescription (right eye: $-3.00 + 1.75 \times 76$ left eye: $-2.50 + 1.50 \times 95$) confirmed a bitemporal visual field defect (Fig. 2A). However, confrontation visual fields were full. Brain magnetic

![FIG. 2. Automated visual fields. A. Bitemporal field loss is present with the patient wearing her reading prescription. B. Visual fields are full with the patient wearing her distance prescription.](image)

![FIG. 3. T2 axial magnetic resonance imaging reveals ovoid globes nasally.](image)

![FIG. 4. A. The black line indicates an emmetropic eye, where parallel light is focused onto the retina. The dashed line indicates a myopic eye, where light is focused anterior to the retina. B. In a myopic eye, with use of a concave lens, parallel light is focused onto the retina. In a patient with no staphyloma, the curvature of the eye is spherical. Light falling onto all parts of the retina will be focused through the concave lens. C. In a patient with staphyloma, light is focused on the macula (solid line) but with increased axial length in the staphylomatous segment, light is not focused on the retina (dashed line) causing blurred vision in the corresponding visual field. P, principal plane of the eye. Modified from Elkington AR, Frank HJ, Greaney MJ (6).](image)
resonance imaging revealed no abnormalities along the visual pathways but did demonstrate “ovoid” globes (Fig. 3). Optical coherence tomography and B-scan ultrasonography confirmed nasal staphylomata in both eyes and showed the eyes to be longer from front to back nasally (29.06 mm, right eye, and 31.40 mm, left eye) than temporally (27.74 mm, right eye, and 29.04 mm, left eye) The diagnosis of refractive bitemporal visual field defects due to staphylomata was confirmed by repeating the examination with the patient wearing her distance refraction, which abolished the field defects (Fig. 2B).

A posterior staphyloma is a protrusion of the posterior wall of the eye (2), commonly associated with high myopia (3), and is known to give rise to visual field defects (4,5). One possible explanation is that nerve fibres are under mechanical tension in the area of the staphyloma which reduces axonal flow impairing optic nerve function (5). An alternate explanation is that the field defects are due to a differing refractive error in the location of the staphyloma caused by increased axial length (6). Our findings support the latter possibility; we repeated visual field testing with a higher power of the correcting lens, compensating for the staphylomata refractive error. Light previously defocused over the staphyloma was now in focus and therefore perceived by the patient (Fig. 4).

Although a rare cause, bilateral nasal staphylomata should be included in the differential diagnosis of bitemporal hemianopia. Unnecessary imaging to rule out compressive lesions of the optic chiasm could have been avoided by retesting fields with a different refractive correction. Clues to diagnosis were bilateral nasal retinal pallor, visual field defects crossing the vertical midline, and the presence of full fields to confrontation.

**Reduced Apparent Diffusion Coefficient in Neuromyelitis Optica–Associated Optic Neuropathy**

In their excellent review of neuromyelitis optica (NMO), Morrow and Wingerchuk (1) discuss the criteria that distinguish this condition from multiple sclerosis. Here, we describe diffusion-weighted magnetic resonance imaging (DWI) of the optic nerve in a patient with NMO-associated optic neuropathy.

A 21-year-old man developed vision loss in the right eye that was diagnosed as optic neuritis. After a delay of 5 months, he was referred for neuro-ophthalmology evaluation. Visual acuity was 20/400 in the right eye and 20/20 in the left eye. Visual field testing showed severe depression in the right eye and normal function in the left eye. The right optic disc was pale and the left optic disc appeared normal. Magnetic resonance imaging (MRI) revealed slight atrophy of the right optic nerve, but no demyelinating plaques. A year later, the patient experienced rapidly progressive vision loss in the left eye. The acuity was 20/400 in the right eye and 20/800 in the left eye, with generalized visual field loss in the left eye. The right optic disc was pale and the left optic disc was edematous. The patient was treated intravenously with methylprednisolone, followed by oral prednisone. Serum and cerebrospinal fluid were positive for anti-AQP4 immunoglobulin G, as determined by a cell-based fluorescence assay (2). Three weeks later, acuity in the left eye was 20/80, with improvement in the visual field.

MRI of the orbits 4 weeks after the onset of vision loss showed enhancement of the left optic nerve (Fig. 1A), and DWI revealed increased signal along the course of the left optic nerve (Fig. 1B). The apparent diffusion coefficient (ADC) map demonstrated hypointense signal within the left optic nerve (Fig. 1C). The ADC value along a representative 45.6 mm² segment of the left optic nerve measured 0.875 × 10⁻³ mm²/s and along a 48.4 mm² segment of the right optic nerve was 1.63 × 10⁻³ mm²/s. DWI obtained a year earlier, The authors report no conflicts of interest.

**ACKNOWLEDGMENTS**

The authors thank Dr Raveesh Hanasoge, MD, DNB, FRCR, for help with MRI images.

**REFERENCES**


Anjali Gupta, MBChB
Victoria Eye Unit, Wye Valley NHS Trust, County Hospital, Hereford, United Kingdom

J. M. Alaric Smith, MBChB, MRCP, FRCOphth
Victoria Eye Unit, Wye Valley NHS Trust, County Hospital, Hereford, United Kingdom

The authors report no conflicts of interest.

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**Letters to the Editor**

**Reduced Apparent Diffusion Coefficient in Neuromyelitis Optica–Associated Optic Neuropathy**

In their excellent review of neuromyelitis optica (NMO), Morrow and Wingerchuk (1) discuss the criteria that distinguish this condition from multiple sclerosis. Here, we describe diffusion-weighted magnetic resonance imaging (DWI) of the optic nerve in a patient with NMO-associated optic neuropathy.

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MRI of the orbits 4 weeks after the onset of vision loss showed enhancement of the left optic nerve (Fig. 1A), and DWI revealed increased signal along the course of the left optic nerve (Fig. 1B). The apparent diffusion coefficient (ADC) map demonstrated hypointense signal within the left optic nerve (Fig. 1C). The ADC value along a representative 45.6 mm² segment of the left optic nerve measured 0.875 × 10⁻³ mm²/s and along a 48.4 mm² segment of the right optic nerve was 1.63 × 10⁻³ mm²/s. DWI obtained a year earlier,
when visual function in the left eye was normal, yielded an ADC in the left optic nerve of $1.03 \times 10^{-3}$ mm$^2$/s.

In patients with NMO, immunohistochemical analysis of lesions has shown local depletion of aquaporin-4 channels (3,4). Loss of AQP4 channels in the optic nerve may contribute to the reduction of water movement. It remains to be determined if our finding of restricted diffusion will be replicated in other patients with NMO-optic neuropathy. A broader issue is whether DWI will prove useful in differentiating different types of optic neuropathy. It has been proposed that DWI may disentangle ischemic optic neuropathy from optic neuritis, which can have overlapping clinical profiles (5). In a recent study, DWI was abnormal in 5/5 patients with acute ischemic optic neuropathy, but only in 2/25 patients with acute optic neuritis (6). However, other studies have concluded that impaired diffusion is a common feature in optic neuritis (7,8). Further MR studies are needed to clarify the prevalence, time course, and correlation with severity of findings of DWI abnormalities in ischemic optic neuropathy, optic neuritis, and NMO-optic neuropathy.

Jonathan C. Horton, MD, PhD  
Departments of Neurology and Ophthalmology  
University of California  
San Francisco, California

Vanja C. Douglas, MD  
Department of Neurology  
University of California  
San Francisco, California

Soonmee Cha, MD  
Department of Radiology  
University of California  
San Francisco, California

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The authors report no conflicts of interest.

REFERENCES

Bilateral Sixth Nerve Palsies in Anti-Aquaporin 4 Antibody Syndrome

While optic neuritis and myelitis are classically described in neuromyelitis optica (NMO), Morrow and Wingerchuk (1) point out other sites within the central nervous system that may be affected. However, despite frequent involvement of the brainstem in NMO, detailed descriptions of the patterns of ophthalmoplegia are available in only a few case reports (Table 1). We report bilateral fascicular sixth nerve palsies in a patient with anti-aquaporin 4 (AQP4) antibody.

A 26-year-old woman complained of headache, vertigo, and unsteadiness. Examination showed spontaneous left-beating nystagmus, gaze-evoked nystagmus (GEN) and leftward falling during walking. Brain magnetic resonance imaging (MRI) revealed a lesion involving the dorsal medulla. Serum anti-AQP4 antibody test was positive. She experienced marked improvement after a 5-day course of corticosteroids. One year later, the patient experienced another episode of headache, somnolence, and visual blurring. Examinations 1 week later showed small amplitude, spontaneous nystagmus beating rightward and upward only without fixation, and impaired vertical smooth pursuit. Brain MRI showed newly developed lesions involving the hypothalamus, mammillary bodies, and optic tracts. Three months later, the patient had the third episode of headache, facial numbness, and diplopia. Examination showed limitation of abduction in both eyes, upbeat nystagmus during convergence, and horizontal and vertical GEN (See Supplemental Digital Content, Video, http://links.lww.com/WNO/A131). Brain MRI disclosed new lesions in the pontine tegmentum bilaterally (Fig. 1).

She was treated with intravenous steroids for a week followed by oral maintenance.

Our patient had recurrent neurological episodes due to lesions involving the dorsal medulla, hypothalamus, mammillary bodies, optic tracts, and dorsal pons, all of which highly express AQP4 (7). Since the discovery of anti-AQP4 antibody as a pathogenic marker of NMO, there has been increasing recognition of patients developing neurologic symptoms and signs attributable to anti-AQP4 antibody, but without optic nerve or spinal cord involvement. Those cases have been termed NMO spectrum disorder to which our patient belongs (8).

We are unaware of previous reports of bilateral fascicular sixth nerve palsies in association with anti-AQP4 antibody. Demyelinating disorders may cause sixth nerve palsy, usually in the setting of multiple sclerosis or chronic inflammatory polyneuropathy (9). In addition to bilateral abduction defects, our patient reported facial numbness, indicating involvement of the spinal trigeminal nucleus and tract. The GEN and convergence-evoked upbeat nystagmus suggest that nearby pontine structures for gaze holding such as the nucleus prepositus hypoglossi and paramedian tract cell groups also were affected (10,11).

Jin-Ah Kim
Seoul National University College of Medicine, Seoul, Korea

Sung-Hee Kim, MD
Department of Neurology, Seoul National University College Medicine, Seoul National University Bundang Hospital, Seongnam, Korea

FIG. 1. Axial fluid-attenuated inversion recovery (FLAIR) magnetic resonance scans show symmetric lesions involving the periventricular pontine region.
### TABLE 1. Ophthalmoplegia in anti-AQ4 antibody syndrome

<table>
<thead>
<tr>
<th>Report</th>
<th>Diagnosis</th>
<th>Gender/Age</th>
<th>Ophthalmoplegia</th>
<th>Other Antibodies</th>
<th>Lesion</th>
<th>Accompanying Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilmore et al (2)</td>
<td>NMO</td>
<td>F/37</td>
<td>Dorsal midbrain syndrome (eyelid retraction, upgaze palsy, convergence-retraction nystagmus, impaired convergence)</td>
<td>Periaqueductal gray matter</td>
<td></td>
<td>Oscillopsia</td>
</tr>
<tr>
<td>Shinoda et al (3)</td>
<td>NMOSD</td>
<td>F/19</td>
<td>Wall-eyed INO</td>
<td>Antinuclear Ab Anti-SS-A Ab</td>
<td>Midbrain tegmentum</td>
<td>Double vision, Dysphagia, Dysarthria, Right-sided weakness Paresthesia</td>
</tr>
<tr>
<td>Garcia-Martin et al (4)</td>
<td>NMO</td>
<td>F/32</td>
<td>INO</td>
<td>Anti-DNA Ab</td>
<td>Brainstem</td>
<td>Vertical diplopia, Paresthesia</td>
</tr>
<tr>
<td>Ogasawara et al (5)</td>
<td>NMOSD</td>
<td>F/62</td>
<td>4th nerve palsy, nuclear</td>
<td></td>
<td>Midbrain, pons, medulla Spinal cord (C5-T1)</td>
<td>Vertical diplopia, Paresthesia</td>
</tr>
<tr>
<td>Lee et al (6)</td>
<td>NMOSD</td>
<td>F/60</td>
<td>Dorsal midbrain syndrome (vertical gaze palsy, convergence spasm, light-near dissociation of the pupil, convergence-retraction nystagmus)</td>
<td>Anti-SS-A Ab Periaqueductal mesodiencephalon</td>
<td></td>
<td>Diplopia, Dizziness, Dry mouth and eyes</td>
</tr>
<tr>
<td>Current Case</td>
<td>NMOSD</td>
<td>F/26</td>
<td>Bilateral 6th nerve palsies Gaze-evoked nystagmus Convergence-evoked upbeat nystagmus</td>
<td>Pons</td>
<td>Pons</td>
<td>Horizontal diplopia, Headache, Dizziness, Nausea, Facial numbness</td>
</tr>
</tbody>
</table>

INO, internuclear ophthalmoplegia; NMO, neuromyelitis optica; NMOSD, neuromyelitis optica spectrum disorder.
Hyo-Jung Kim, PhD
Department of Biomedical Laboratory Science,
Kyungdong University,
Goseong, Korea

Ji-Soo Kim, MD, PhD
Department of Neurology,
Seoul National University College Medicine,
Seoul National University Bundang Hospital,
Seongnam, Korea

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Torsten Müller, Emil Reif. Thieme. 2014. $47.99
ISBN: 978-3-13-1255044

Head and Neck anatomy is essential to the diagnosis of many neuro-ophthalmic conditions. The ability to localize pathology corresponding to clinical findings and corroborate that with imaging studies is central to patient care. Localizing and diagnosing conditions with the help of imaging can expedite the treatment process and allow for better prognosis.

The 333 pages of this book are divided into 3 major sections: 1) cranial computed tomography, 2) cranial magnetic resonance imaging, and 3) neck. The book is organized such as the left page has the radiologic image along with a picture representation of the level of the image and the right page has a full color diagram corresponding to the radiologic image with detailed anatomic structures presented in a numbered format with an accompanying legend. For example, great representations of cavernous sinus anatomy, with all structures labeled through different levels, are presented. Orbital anatomy is also clearly delineated. Other helpful pearls throughout the book include great representation of bony anatomy and a summary of vascular territories. Axial, coronal, and sagittal cuts are represented in each section.

This book is a concise anatomical guide with correlation between radiologic imaging and corresponding diagrams detailing different structures at various levels and cuts. There is no pathology represented, and all images are of normal anatomy. It serves as a good reference for students and physicians reviewing head and neck imaging.

Lina Nagia
Department of Ophthalmology
University of Alabama School of Medicine, Birmingham, AL
lnagia@uab.edu
Neuro-Ophthalmology in Hungary

Judit Somlai, MD

History

In the 1960s, neuro-ophthalmology in Hungary began in the Neurology Clinic of Semmelweis University (Budapest), with the collaboration of Dr. Istvan Olah, a neuro-ophthalmologist, and Dr. Bela Horanyi, a neurologist. It was from this point forward that the importance of ophthalmic symptoms in neurologic disorders was emphasized, both in clinical practice and in medical education.

At the same time, at the National Institute of Neurosurgery, Dr. Laszlo Remenar, an ophthalmologist and orbital surgeon, founder of orbital surgery in Hungary, cooperated with neurosurgeons, and they operated on the same team in orbitocranial diseases. The Hungarian National Institute of Neurosurgery worked in close cooperation with Dr. Alfred Huber at the Center for Neurosurgery in Zurich, Switzerland.

In 1987, at the National Institute of Psychiatry and Neurology, Dr. Judit Somlai began a neuro-ophthalmology unit under the supervision of Dr. Peter Halász, professor of neurology. The Institute was closed in 2004, and Dr. Somlai now practices at the Military Hospital.

Education

Beginning in 1995, neuro-ophthalmology became a part of neurology education at all medical schools in Hungary. This has led to an increased awareness and interest in neuro-ophthalmology, and now a specific licensing process takes place for the subspecialty. This includes completion of medical school, passing specialty examinations in neurology and/or ophthalmology, and then a 1-year neuro-ophthalmology fellowship at an accredited medical school, with an additional licensing examination required.


Table 1 lists all neuro-ophthalmologists in Hungary, including the city in which they practice and their academic affiliation. A number of these individuals have been active in the International Neuro-Ophthalmology Society (INOS) and the European Neuro-Ophthalmology Society (EUNOS).

The first update meeting in the history of EUNOS took place in Budapest in April 2012, organized by Gabriella Szatmáry (http://www.dremed.com/medical-trade-shows/?p=1273). In 2017, the annual congress of EUNOS will be held in Budapest.

Table 2. Hungarian neuro-ophthalmology textbooks

<table>
<thead>
<tr>
<th>Author</th>
<th>Title</th>
<th>Publisher</th>
<th>ISBN</th>
</tr>
</thead>
</table>

Handbooks

In addition, a number of neuro-ophthalmology textbooks have been published in Hungary and are listed in Table 2 including a recent edition of the Handbook of Neuro-Ophthalmology, edited by Drs. Somlai and Kovacs (Fig. 1).

World Congress on Controversies in Neurology

The Ninth World Congress on Controversies in Neurology (CONy) will take place in Budapest, March 26–28, 2015 (http://www.comtecmed.com/Cony/2015/).

For the first time, a session will be devoted to neuro-ophthalmology. This will be organized by Dr. Judit Somlai.
and will cover a variety of topics, including insights into the pathophysiology of nonarteritic anterior ischemic optic neuropathy and discussions on pseudotumor cerebri, idiopathic intracranial hypertension, and the controversy surrounding venous sinus stenosis with raised intracranial pressure.

Although Hungary is a small country composed of 10 million people, the last 50 years have seen great advances in clinical practice and medical education in neuro-ophthalmology. The future seems very bright for our subspecialty in Hungary in the years to come.
Neuro-Ophthalmology in China

Xiaojun Zhang, MD, PhD

One of the earliest Chinese neuro-ophthalmic publications appeared in the Chinese Medical Journal in 1932 and dealt with optic disc abnormalities. It was authored by Dr. Wenbing Lin (Fig. 1), a graduate of Harvard Medical School who returned to Shanghai in 1926. In subsequent years, articles dealing with retrobulbar optic neuritis were published by ophthalmologists in Shanghai and Chengdu. In 1949, Dr. Yuanxiu Lao (Fig. 2) spent 1-year training in neuro-ophthalmology and visual field testing at the University of Pennsylvania with Francis H. Adler, MD and Harold G. Scheie, MD. She returned to China in 1950 and started the first neuro-ophthalmology service at Peking Union Medical College Hospital. In 1957, she published Clinical Perimetry, the first Chinese textbook dealing with evaluation of visual fields. In 1958, the first Chinese neuro-ophthalmology textbook entitled Clinical Neuro-ophthalmology was published. It was coauthored by a senior neurosurgeon Zhesheng Han, and ophthalmologist, Xiaohui Zheng.

Advances in our subspecialty slowed in 1966 with the start of the cultural revolution and lasted 10 years. In 1979, Dr. Mi Yan (Fig. 3) did a retinal fellowship at Scheie Eye Institute, University of Pennsylvania followed by a neuro-ophthalmology fellowship at Wilmer Eye Institute, John Hopkins Hospital in Baltimore. Dr. Yan returned to China and established the first neuro-ophthalmology clinic at West China School of Medicine University in Chengdu, Sichuan. He also introduced neuro-ophthalmology to more ophthalmologists at the annual National Training Course of Ocular Fundus Disease which began in 1988. Ten years later, Dr. Yan was instrumental in creating a neuro-ophthalmology section in the Chinese Journal of Ocular Fundus Disease. In addition, articles dealing with optic neuritis, Leber hereditary optic neuropathy, and other neuro-ophthalmic disorders began to appear in the English literature. During this period, textbooks were published in Chinese including Clinical Practical Neuro-Ophthalmology coauthored by senior ophthalmologist, Dr. Yi Tong from Fujian Medical University and Japanese ophthalmologist, Tadashi Fujino, and Neuro-ophthalmology authored by a senior neurologist, Chunhe Zhai from Shanghai.

In the past decade, many Chinese ophthalmologists and neurologists received training abroad, and neuro-ophthalmology in China has experienced rapid growth (Table 1). Xinzu Gu, after finishing his training in Doheny Eye Institute in Los Angeles, established a neuro-ophthalmology service in Zhongshan Eye Center in Guangzhou in 2002, with a research interest in pupillary disorders. Xiaojun Zhang completed a neuro-ophthalmology fellowship at the Emory Eye Center in Atlanta and returned to Beijing in 2005. Dr. Zhang set up the first multidisciplinary neuro-ophthalmology center with both an outpatient clinic and a 40-bed inpatient unit at Beijing Tongren Hospital. Master and PhD degree programs in neuro-ophthalmology were created in the Department of Neurology of Beijing Tongren Hospital, Capital Medical University, and now there are 12 graduates who work in different teaching hospitals in China.

Currently, there are 9 university hospitals that have neuro-ophthalmology clinics, mostly based on ophthalmology departments (Table 2). Neuro-ophthalmologists in these hospitals usually combine their practices with other...
subspecialties, such as retina, strabismus, cataract, electrophysiology, or neurological subspecialties. Neuro-ophthalmology services outside of these university hospitals are provided by general ophthalmologists.

Currently, neuro-ophthalmology is not a mandatory part of residency training in either ophthalmology or neurology, and there are no neuro-ophthalmology fellowship training programs. This has led to creation of short-term training courses in neuro-ophthalmology. In 2003, first national neuro-ophthalmology training course was hosted by Dr. Xinzu Gu. Dr. Yong Zhong from Peking Union Medical Hospital and Dr. Shi hui Wei from the People’s Liberty Army General Hospital also annually run national training courses. In April 2011, a 2-day intensive training course named Chinese National Key Neuro-ophthalmologist Training Course was held and attracted over 100 attendees. The content was prepared by Jonathan Trobe, and the conference was led by Xiaojun Zhang and Shi hui Wei. This has become the only national annual neuro-ophthalmology training course in China. In addition, many neuro-ophthalmologists have lectured in China including Neil Miller, Joseph Rizzo, Peter Savino, Andrew Lee, Valerie Biousse, Agnes Wong, Gondon Plant, Satoshi Kashii, and May-Yung Yen. Bradley Farris has been giving his training course on optic nerve sheath fenestration in Chengdu annually for over 10 years. Table 3 shows the major neuro-ophthalmology research programs in China. Although most studies are published in the Chinese literature, Chinese neuro-ophthalmologists now are presenting their research findings at international meetings and more publications are appearing in English language journals.

The Chinese Ophthalmology Society (COS) annual meeting is held in each fall. Since 2007, there has been a neuro-ophthalmology session at this meeting. In 2012, the COS approved creation of the Chinese Neuro-ophthalmology Society (CNOS). This was followed by a joint conference of the inaugural CNOS meeting and the 2nd National Key Neuro-ophthalmologist Training Course. Held in Beijing, with over 400 attendees, invited lecturers included Satoshi Kashii (Aichi, Japan), An-Guor Wang (Taipei, Taiwan), Patrick Yu-Wai-Man (Newcastle, United Kingdom), Ian Morgan (Canberra, Australia), and David and Sheila Crewther (Melbourne, Australia). The most recent CNOS annual meeting was held this June in Suzhou, Zhejiang, combining Jonathan Trobe’s Training course and The Cross-Strait Neuro-ophthalmology symposium. The 8th annual meeting of the Asian Neuro-Ophthalmology Society will be held in October 2015 in Beijing.
**TABLE 1.** Chinese neuro-ophthalmologists trained in the United States

<table>
<thead>
<tr>
<th>Name/City</th>
<th>Training Background</th>
<th>Mentor/City</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yuanxiu Lao (deceased)</td>
<td>Ophthalmologist</td>
<td>Harold G. Scheie/Philadelphia</td>
</tr>
<tr>
<td>Mi Yan (deceased)</td>
<td>Ophthalmologist</td>
<td>Harold G. Scheie/Philadelphia; Neil Miller/Baltimore</td>
</tr>
<tr>
<td>Xinzu Gu/Guangzhou</td>
<td>Ophthalmologist</td>
<td>Alfredo A. Sadun/Los Angles</td>
</tr>
<tr>
<td>Xiaojun Zhang/Beijing</td>
<td>Neurologist</td>
<td>Nancy Newman; Valerie Biousse/Atlanta</td>
</tr>
<tr>
<td>Xuxiang Zhang/Beijing</td>
<td>Ophthalmologist</td>
<td>Byron Lan/Miami; David Zee/Baltimore</td>
</tr>
<tr>
<td>Tao Fu/Beijing</td>
<td>Ophthalmologist</td>
<td>Agnes Wong/Toronto</td>
</tr>
<tr>
<td>Hui Chen/Chengdu</td>
<td>Ophthalmologist</td>
<td>Bradley K. Farris/Oklahoma City</td>
</tr>
<tr>
<td>Guohong Tian/Shanghai</td>
<td>Neurologist</td>
<td>Joseph Rizzo/Boston</td>
</tr>
</tbody>
</table>

**TABLE 2.** Neuro-ophthalmology clinics in university hospitals in China

<table>
<thead>
<tr>
<th>Department/Institute/Hospital</th>
<th>Directors/Leaders</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Department of Ophthalmology, Peking Union Medical College Hospital</td>
<td>Yong Zhong, MD, PhD (Ophthalmologist)</td>
<td>Beijing</td>
</tr>
<tr>
<td>2. Eye Center, West China Hospital, West China Medical School</td>
<td>Fang Lu, MD, PhD</td>
<td>Chengdu, Sichuan</td>
</tr>
<tr>
<td>3. Zhongshan Eye Hospital, Zhongshan Medical University</td>
<td>Xinzu Gu, MD, PhD; Changxiang Yi, MD, PhD</td>
<td>Guangzhou, Guangdong</td>
</tr>
<tr>
<td>4. Department of Ophthalmology, Fujian Medical University No. 1 Hospital</td>
<td>Yi Tong, MD</td>
<td>Fuzhou, Fujian</td>
</tr>
<tr>
<td>5. Department of Neurology, Eye Center, Beijing Tongren Hospital, Capital Medical University</td>
<td>Xiaojun Zhang, MD, PhD; Weibin Wei, MD, PhD</td>
<td>Beijing</td>
</tr>
<tr>
<td>6. Department of Ophthalmology, the People’s Liberty Army General Hospital</td>
<td>Shi hui Wei, MD</td>
<td>Beijing</td>
</tr>
<tr>
<td>7. Department of Ophthalmology, Shanghai Eye &amp; ENT Hospital, Fudan University</td>
<td>Min Wang MD, PhD; Guohong Tian, MD, PhD</td>
<td>Shanghai</td>
</tr>
<tr>
<td>8. Department of Neurology, Ophthalmology, Beijing Xuanwu Hospital, Capital Medical University</td>
<td>Xuxiang Zhang, MD, PhD</td>
<td>Beijing</td>
</tr>
<tr>
<td>9. Department of Ophthalmology, Xijing Hospital, the 4th Military Medical University</td>
<td>Siwei You, MD, PhD</td>
<td>Xi-an, Shanxi</td>
</tr>
</tbody>
</table>

**TABLE 3.** Current research programs in neuro-ophthalmology in China

<table>
<thead>
<tr>
<th>Research</th>
<th>Primary Investigators</th>
<th>Group and Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mt-DNA mutation and clinical features of Leber hereditary optic neuropathy</td>
<td>Yi Tong; Jia Qu</td>
<td>Department of ophthalmology, Fujian Medical University, Fuzhou, China (South-east China)</td>
</tr>
<tr>
<td>Optic neuritis</td>
<td>Xiaojun Zhang</td>
<td>Department of Neurology, Beijing Tongren Hospital, Capital Medical University, Beijing, China (North China)</td>
</tr>
<tr>
<td>Ocular myasthenia gravis</td>
<td>Shi hui Wei</td>
<td>Department of Ophthalmology, People Liberty Army General Hospital, Beijing, China (North China)</td>
</tr>
<tr>
<td>Nonarteritic anterior ischemic optic neuropathy</td>
<td>Xiaojun Zhang; Yun Jing; Lei Yu</td>
<td>Department of Neurology, Department of thoracic Diseases, Beijing Tongren Hospital, Beijing, China (North China)</td>
</tr>
<tr>
<td>Normal tension glaucoma and intracranial pressure</td>
<td>Run-sheng Wang</td>
<td>Department of Ophthalmology, Xi-an No. 4 Hospital, Xi’an, China (West China)</td>
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<td>Qiping Wei</td>
<td>Department of Ophthalmology, Dongfang Hospital, University of Chinese Traditional Medicine and Pharmacology, Beijing, China (North China)</td>
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Clearly, momentum in neuro-ophthalmology in China is increasing. With access to worldwide communication, help from colleagues and friends, enthusiasm and effort of a younger generation, neuro-ophthalmology in China will develop even more rapidly in the years to come.

Xiaojun Zhang, MD, PhD
Department of Neurology, Beijing Tongren Hospital, Capital Medical University, Beijing, China

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