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On occasion, it is important to step out of your comfort zone and look critically at accepted dogma. That is the purpose of this editorial. Although not dealing directly with our subspecialty, statistics play an important role in how we interpret the literature. There is currently an ongoing debate by statisticians as to what are the best metrics and methods to assess clinical studies. As evidenced here, P values are not the ultimate test of scientific legitimacy, but rather only one (controversial, imperfect) recognized tool for evaluating experimental results.

Value of the P Value

Jack Parker, MD, Carrie Huisingh, MPH, Gerald McGwin Jr, MS, PhD

In modern medical research, P values have become, in the minds of many, the most important indicator of the truth of a scientific proposition and the key instrument differentiating "real" effects from those due to "random chance." Consequently, it is no exaggeration to say that the landscape of medical research has been decisively shaped by a pervasive belief in the power of P values. They have come to determine not only which studies are published but also which projects are funded and which ideas pursued. It is, therefore, shocking to many physicians to learn that a legitimate suspicion exists among statisticians regarding the real usefulness of P values, particularly as a stand-alone measure of validity. This skepticism has its roots in, of all places, the Guinness brewery, the birth place of P values and the concept of statistical significance. In 1908, William Sealy Gosset, head experimental brewer for Guinness Beer in London and mathematician, published an article on "statistical significance," in which he endeavored to explain how to determine which inputs in the brewing process made the greatest difference in the quality of the drink. Nevertheless, in this article, Gosset wrote, "The important thing is to have a low real error, not to have a 'significant' result at a particular station. The latter seems to me to be nearly valueless in itself" (1). Another statistician of the time, Ronald Fisher, is often credited with the ubiquitous use of 5% as the benchmark for scientific legitimacy although this is often based on a misunderstanding of Gosset work. Debates between Fisher and 2 other statisticians of the time, Jerzy Neyman and Egon Pearson, perhaps best illustrate the controversy regarding the P value; is it an absolute measure to be interpreted in context or one either above or below a prespecified benchmark, typically 5%?

These debates regarding the use of P values have been inherited by subsequent generations of statisticians; yet, as with many traits that are passed from one generation to the next and become muted with time, P values are frequently misinterpreted and vastly misunderstood (2–7). When asked to explain a P value a not uncommon response is "It is the probability that the null hypothesis is true." This is incorrect. In fact, it is the exact opposite of the truth. This is because the operating principle of the P value is the assumption that the null hypothesis is correct, that is, there is no real effect of a given intervention. Therefore, the information provided by P values is the probability of the data, given the assumption that the intervention is ineffectual. As a result, the P value provides no information (and makes no attempt) to inform about the probability of null hypothesis.

Another misconception is that the P value <0.05 is "statistically significant" and therefore must be clinically important. This is not correct for several reasons. First, the difference may be too small to be clinically meaningful. The P value carries no information about the magnitude of the effect and
precision of the estimate, which are captured by the point estimate and the confidence interval. A very small $P$ value such as $<0.01$ does not necessarily mean a strong association (8,9). The strength of the association comes from the effect size, which is a measure of the strength of the relationship between 2 variables (e.g., odds ratio, relative risk, and correlation coefficient) (10). Second, the end point itself may not be clinically important (e.g., use of surrogate outcomes). Third, it is possible to achieve a $P$ value $<0.05$ simply by changing the sample size of the sample.

A far greater problem arises from misinterpretation of nonsignificant findings. A $P$ value $>0.05$ is often called “nonsignificant.” The term “nonsignificant” wrongly implies that the study has shown that there is no difference between groups and that a nonsignificant $P$ value is a good evidence of a true null hypothesis (4). This does not mean that the treatment is not beneficial; only that the possibility of chance producing a difference of this size is so large that it is impossible to demonstrate the “significance” of the treatment effect. Although it is usually reasonable not to accept a new treatment unless there is positive evidence in its favor, when issues of public health are concerned, the absence of evidence is not always valid justification for inaction (4). Rather, other evidence is needed to appropriately accept the null hypothesis as true. The magnitude of the association and confidence intervals that can help researchers make an informed interpretation (11). The other problem is that this terminology perpetuates the idea that the results must fall on one side or another of a demarcation as if the study conclusively proved whether a certain phenomenon existed when, in reality, one of the established beliefs of modern biomedical statistics is that results are simply statistically significant or not (10,12,13).

Having described what a $P$ value is not, the question remains what is a $P$ value? A $P$ value is a probability of obtaining a result at least as extreme as the observed results in a study, when the null hypothesis is really true (14). A $P$ value is a continuous measure with a uniform distribution ranging from zero to one; however, the $P$ value conventionally is dichotomized at 0.05. If the $P$ value is below 0.05, the null hypothesis is rejected and the observed results are called “significant.” A $P$ value $<0.05$ is an arbitrary cut-point for a statistic that captures one of many possible sources of error, so the correct evaluation of a $P$ value is fundamentally a qualitative process. Moreover, it is but one of several pieces of information that should be used to interpret the results of scientific research, the magnitude of the effect and the associated, typically 95% confidence interval. Taken together, this information provides the researcher, and perhaps more importantly, the scientific community and the public, a more robust perspective on a study’s results. They allow us to appropriately dismiss statistically significant results associated with clinically meaningless effect sizes while advancing nonsignificant results wherein the effect size was large. The value of $P$ values is not their ability to serve as an isolated, easily understood, scientific seal of approval; rather, they are but one piece of scientific evidence that, when properly applied and combined with all other available evidence, can be used to begin a conversation regarding the proper interpretation of a study’s results.

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Adding Vision to Concussion Testing: A Prospective Study of Sideline Testing in Youth and Collegiate Athletes

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Background: Sports-related concussion commonly affects the visual pathways. Current sideline protocols test cognition and balance but do not include assessments of visual performance. We investigated how adding a vision-based test of rapid number naming could increase our ability to identify concussed athletes on the sideline at youth and collegiate levels.

Methods: Participants in this prospective study included members of a youth ice hockey and lacrosse league and collegiate athletes from New York University and Long Island University. Athletes underwent preseason baseline assessments using: 1) the King-Devick (K-D) test, a <2-minute visual performance measure of rapid number naming, 2) the Standardized Assessment of Concussion (SAC), a test of cognition, and 3) a timed tandem gait test of balance. The SAC and timed tandem gait are components of the currently used Sport Concussion Assessment Tool, 3rd Edition (SCAT3 and Child-SCAT3). In the event of a concussion during the athletic season, injured athletes were retested on the sideline/rink-side. Nonconcussed athletes were also assessed as control participants under the same testing conditions.

Results: Among 243 youth (mean age 11 ± 3 years, range 5–17) and 89 collegiate athletes (age 20 ± 1 years, range 18–23), baseline time scores for the K-D test were lower (better) with increasing participant age (P < 0.001, linear regression models). Among 12 athletes who sustained concussions during their athletic season, K-D scores worsened from baseline by an average of 5.2 seconds; improvement by 6.4 seconds was noted for the nonconcussed controls (n = 14). The vision-based K-D test showed the greatest capacity to distinguish concussed vs control athletes based on changes from preseason baseline to postinjury (receiver operating characteristic [ROC] curve areas from logistic regression models, accounting for age = 0.92 for K-D, 0.87 for timed tandem gait, and 0.68 for SAC; P = 0.0004 for comparison of ROC curve areas).

Conclusions: Adding a vision-based performance measure to cognitive and balance testing enhances the detection capabilities of current sideline concussion assessment. This observation in patients with mild traumatic brain injury reflects the common involvement and widespread distribution of brain pathways dedicated to vision.


Concussion results from an impulsive blow to the body or head and produces functional injury to the brain. Consequences include a variety of neurological symptoms, including many related to vision (1–7). Recent data show that both high school and collegiate athletes underreport concussion symptoms and sequelae (3, 4). The frequent lack of overt signs of concussion, along with pressures to return to play, makes certain athletes more vulnerable to competing with a brain injury. The development of rapid objective screening tools for concussion diagnosis may remove some of the guesswork required when relying solely on symptoms reported by the athlete.

A number of sideline assessments have been identified to distinguish athletes with concussion after acute injury. The Standardized Assessment of Concussion (SAC) (8, 9) and...
the Balance Error Scoring System (BESS) are commonly used at the collegiate level (10, 11). The Sport Concussion Assessment Tool, 3rd Edition (SCAT3) combines both cognitive and balance testing, including the SAC and a modified BESS or timed tandem gait test (11, 12). Child-SCAT3, a battery similar to SCAT3, is recommended for use of athletes younger than 13 years and is under investigation. The combination of SAC and BESS (cognitive and balance testing) has been used to help diagnose concussion on the sidelines in collegiate cohorts (12). However, this composite of tests lacks a vision-based performance measure.

Because approximately 50% of the brain’s circuits are dedicated to vision, the ability to test these pathways may increase our ability to detect concussion after acute injury (2, 13). A study of collegiate athletes suggests that adding a vision-based test of rapid number naming to the SAC and BESS allows for identification of most or all concussions (14). The King–Devick (K-D) test requires intact saccades and other eye movements to perform quickly; literature to date on the K-D test has shown worsening of time scores from a preseason/competition baseline in 60+ concussed athletes (15, 16). Given its simplicity (timed rapid number naming), rapid administration (<1 minute in collegiate athletes), and high test–retest reliability (ICC = 0.96–0.97) (16, 17), the K-D test can be used by nonmedical personnel, including parents—frequently the only adults present on the sidelines for youth sports (18). Having a preseason baseline score for each athlete available in the event of a concussion adds to the simplicity of the K-D test; based on studies in multiple athlete cohorts to date, any worsening (slowing) of the time score from baseline should raise concern (14–16,18–22).

The purpose of this investigation was to examine the vision-based K-D test as a complement to the current SCAT3/Child-SCAT3 measures of cognition (SAC) and balance (timed tandem gait) for sideline diagnosis of concussion. This study is novel in testing in our youngest groups of athletes (youth aged 5–17 years) and in using nonconcussed control athletes as a direct comparison to testing in those with head injury. Because the K-D, SAC, and timed tandem gait are performance measures, we also sought to determine how increasing age may play a role in the time and accuracy for completion of these tests among youth athletes.

METHODS

Study Participants

Study protocols were approved by the Institutional Review Board at the New York University School of Medicine; informed consent and child assent were obtained as appropriate from all participants. Youth and collegiate athletes in this prospective study included participants from the Pelham Youth Hockey Association, NYU Collegiate Athletics, Long Island University (LIU), Pelham Union School District and Pelham Youth Lacrosse. Athletes were aged 5 years and older; boys and girls along with men and women were included. K-D, SAC, and timed tandem gait tests were performed at a preseason baseline as part of this study. Those who sustained a concussion had testing repeated on the sidelines/rink-side as soon as medically feasible. Control athletes playing a similar position who were also consented/assented for the study underwent testing under the same conditions as the concussed athlete. Controls were in place to examine the potential role for fatigue or other factors related to play/practice on test scores in the absence of concussion. Previous studies of the K-D test have demonstrated that vigorous exercise/scrimmage alone is associated with improvements in scores, consistent with learning effects inherent in performance measures in the absence of injury (15, 17).

King–Devick Test

K-D is a test of rapid number naming that takes <1 minute to administer in collegiate athletes; times are slightly longer (<2 minutes) in younger athletes. The test consists of 3 cards with variably spaced single digit numbers (Fig. 1). Participants are asked to read each card as quickly as possible; the time to read each card is recorded. Times for all 3 cards are summed to give a total time score (15, 16,19–22). Higher testing times compared with baseline indicate worsening of performance. Worsening scores are not observed after competition/fatigue alone (15); healthy athletes typically show improvement with exercise (15, 17). Because shorter times are expected in nonconcussed athletes, any worsening of K-D scores from baseline is consistent with concussion. In previous studies investigating the utility of the K-D test, baseline examinations were performed in a noisy hot locker room, and we found no difference in inter- or intra-rater reliability (15). Although these examinations were not performed during game time, they were performed under uncomfortable circumstances. In this study, baseline examinations of the K-D test were also administered for 2 trials to obtain the best possible baseline score.

Standardized Assessment of Concussion

The SAC is a brief cognitive test. A maximum total score of 30 is generated by adding the 4 subscores: Orientation (maximum score = 5), Immediate Memory (maximum score = 15), Concentration (maximum score = 5), and Delayed Recall (maximum = 5). Recent evidence-based guidelines suggested that a worsening of 2–4 points from baseline is a sensitive threshold for clinically meaningful change for SAC (12). We used this threshold as a dichotomous criterion for worsening of the SAC.

Timed Tandem Gait Test

The timed tandem gait is a balance component of the SCAT3 and Child-SCAT3. To perform this test, the participant is instructed to walk along a 38-mm wide,
3-m long sports tape. Athletes place 1 foot in front of the other along the line as quickly and accurately as possible. The best time of 4 trials back and forth along the tape is recorded as the official score. Studies show that dynamic balance and coordination tests, such as timed tandem gait, are less impacted by exercise fatigue than are static balance tasks, such as the BESS (23). Resiliency of dynamic balance testing was reinforced by a study showing that high-intensity exercise decreased performance of both static and dynamic balance testing; timed tandem gait, however, was unaffected by moderate exercise (20).

**Testing Procedures**

Baseline preseason assessments for the sideline tests (K-D, SAC, and timed tandem gait) were performed preseason before practices started. Tests for these sessions were administered by trained study volunteers or by athletic trainers in the case of collegiate athletes. NYU study personnel were present and performed training of testers for baseline assessments. Components of SCAT3 are performed routinely as part of athletic training for collegiate athletes; in the youth athletes, these tests were performed for research purposes as part of this study.

Concussion was defined using the standard definition of witnessed or reported impulse blow to the head or body followed by any neurological symptom(s). Judgments about whether a concussion had occurred were made by athletic trainers for collegiate cohorts. For youth athletes, the judgments of volunteer parents specifically assigned to assess injured athletes at each game/practice were used.
For athletes without witnessed trauma who presented later with symptoms consistent with concussion, testing was performed as soon as possible after the athlete self-reported. The diagnosis of concussion was confirmed in all cases by an expert physician.

**Statistical Analyses**

Statistical analyses were performed using Stata 13.0 (StataCorp, College Station, TX). The Wilcoxon signed-rank test was performed to determine changes in scores from baseline to postinjury. Linear regression models, accounting for age, were used to examine associations of baseline K-D scores to scores for SAC and balance testing. The capacity for each of the tests to distinguish concussed vs nonconcussed control athletes immediately after injury (concussed athlete) was determined by logistic regression models, accounting for age, with calculation of areas under the receiver operating characteristic (ROC) curves. ROC curve areas represent the probability that a test or combination of tests can distinguish concussed athletes vs controls and range from 0.5 (probability no better than chance) to 1.0 (perfect ability to distinguish). Comparisons of the logistic regression-derived ROC curve areas were made for combinations of the 3 tests (K-D, SAC total score, and balance testing) using linear combination methods.

**RESULTS**

Preseason baseline and postinjury test scores are reported in Table 1. There were 243 youth athletes, aged 11 ± 3 (range 5–17 years, 16% female) and 89 collegiate, aged 20 ± 1 (range 18–23 years, 26% female), for a total of 332 participants. Baseline scores for all tests (Table 1) improved with increasing age in this combined cohort (P < 0.001, linear regression models); this age effect was particularly evident for K-D card 3, where vertical crowding of the test numbers is the greatest (P < 0.001 for card 3 vs card 1, linear regression; Fig. 2).

Twelve athletes sustained a concussion during their athletic season. Fourteen control athletes without concussion, matched by youth or collegiate level, were evaluated after competition/practice. For players who had a concussion, changes in scores from baseline were significant for both the K-D test (P = 0.002) and the timed tandem gait (P = 0.02, Wilcoxon signed-rank test, Table 1). Among concussed athletes, K-D worsened from baseline by an average of 5.2 seconds vs improvement by 6.4 seconds for nonconcussed control athletes.

In terms of continuous test scores, K-D showed the greatest capacity to distinguish concussed vs control groups based on changes from preseason baseline ROC curve areas from logistic regression models, accounting for age were K-D = 0.92, timed tandem gait = 0.87, and SAC = 0.68 (P = 0.0004 for comparison of ROC curve areas, Fig. 3A). A composite of tests including SAC, timed tandem gait, and
K-D together (ROC curve area = 0.97) was a greater discriminator of concussed vs control athlete groups than was the combination of SAC and timed tandem gait as used in the SCAT3/Child-SCAT3 (ROC curve area, 0.88, Fig. 3B). The combination of timed tandem gait and K-D (ROC curve area = 0.98) was nearly identical to the composite of 3 tests (ROC area = 0.97). This means that athletic trainers had a 92% probability of correctly distinguishing a concussed vs nonconcussed athlete based on the result of the K-D test alone.

When the test scores were analyzed using published cutoffs for worsening from baseline in the setting of concussion, the SAC showed a 2 point or more worsening (12) in 2/10 concussed players (20%) and 3/14 controls (21%). The timed tandem gait showed worsening in 10/12 concussed players (83%) and 5/14 controls (36%). K-D times demonstrating worsening in 9/12 (75%) concussed players and 1/14 controls (7%).

DISCUSSION

Results of this investigation demonstrate that adding a rapid simple vision-based performance measure to cognitive and balance tests enhances the detection capabilities of current sideline assessments for concussion. Because rapid number naming captures visual function, K-D is a useful tool to aid in the diagnosis of concussed athletes at all levels of sport (14–16,19–22). Use of a measure that requires saccadic eye movements is particularly effective for several reasons. Studies have shown that patients with impaired saccades post-concussion have both cortical and subcortical deficits. These deficits correlate with worse scores for quality of life assessments (24). Saccadic eye movements require relay of information throughout the brain, including frontal eye fields.
supplementary eye fields, dorsolateral prefrontal cortex, intraparietal sulcus, and deeper structures of the brainstem (25–27). Eye movement testing enables the analysis of a number of circuits throughout the brain including visual–spatial integration, motor planning, attention, motivation, and spatial organization (26). The wide distribution of neuronal networks required for saccades thus makes a vision-based sideline screening test particularly effective.

The K-D test has been successful in identifying concussion in boxers and Mixed Martial Arts fighters. In those studies, worse K-D scores were associated with lower scores for the Military Acute Concussion Evaluation, a brief cognitive test, both postfight \((r_s = -0.79, P = 0.0001)\) and regarding changes from prefight baseline \((r_s = 0.90, P < 0.0001)\) (19). Worsening of K-D times was associated with worsening SAC immediate memory scores \((P < 0.001, R^2 = 0.62)\) (16). Studies have shown that K-D scores correlate with Immediate Post-Concussion Assessment and Cognitive Testing (IMPACT) subscores that are visual in nature (14, 17, 28). As an added benefit, the K-D test can accurately and easily be performed by non-medically trained observers, including parents of youth athletes (18).

Another factor that adds to the simplicity and relevance of the K-D test in youth athletes is the use of preseason baseline scores. Baseline scores obviate the need for parents or others on the sidelines to determine normative values in the acute setting of an injury. Furthermore, as shown in this study, K-D time scores decrease (improve) with advancing age of youth athletes. Although these factors make determination of new baseline scores essential at the start of each athletic season, the use of baseline scores eases interpretation when time is of the essence. Using modern definitions, a concussion should be suspected when an athlete has 1) an impulse blow to the head or body and 2) any new neurological symptom. Tests such as K-D, therefore, are used to remove some of the guesswork from this process and should not substitute for clinical or parental judgment that a concussion has occurred.

In our youth athlete cohort, worse scores were noted among younger players for all sideline tests. K-D time scores in particular were significantly slower for younger players \((P < 0.001)\). This association with age and improved overall K-D scores (faster times) could be explained by developmental changes in saccadic eye movements and cognition. Diffusion tensor imaging MRI studies have shown that both white matter and gray matter changes continue in the frontal lobes throughout childhood (29). Eye movement tasks, which require frontal lobe circuits, begin to reach stabilization around adolescence, in concert with other developmental changes in the brain (29).

Saccades have been described by their components: peak velocity, latency, and accuracy. Although changes in velocity of saccadic eye movements with age have been inconsistently described, saccadic latency decreases throughout childhood. Changes in accuracy also stabilize with age (29). Age-related changes in saccade latency and accuracy may extend beyond the oculomotor system and may reflect changes in cognitive processing (29). The K-D test, which requires saccadic eye movements with a superimposed cognitive task, may also be impacted by the normal developmental changes of the brain with age and that may explain the improved times we observed with increasing age.

Performance on test card 3 with the greatest degree of vertical visual crowding had the most variability in terms of testing times. Scores on this card improved with older age within the cohort of athletes younger than 18 years (Fig. 2, \(P < 0.001, \text{linear regression}\)). It is suspected that the effect on this specific card may also be secondary to visual crowding, an age-dependent ability to visualize objects among clutter (30).

Future studies of the K-D test will explore the possibility of age-related norms. In this study, baseline scores for collegiate athletes averaged 38.4 seconds, very similar to collegiate athlete scores in previous studies (average 37.0 seconds, range 36.0–40.2 seconds) (15). Reference ranges for baseline scores in children are under development; these are likely to correlate with age as suggested by our results and by literature suggesting an impact of the changing brain on measures of saccadic eye movement performance (30). Studies are also ongoing to examine the eye movement dynamics and correlates of K-D test performance using formal eye movement recordings. These investigations will determine how prolonged K-D test times may relate to transient slowing of saccades, saccadic inaccuracy, increased latency, or a combination of these factors. The potential role for antisaccades in eye movement-related tasks after concussion will also be examined.

To our knowledge, this is the first investigation to examine the use of timed tandem gait in children. Our data show that the timed tandem gait is a potentially useful tool in the assessment of concussions in youth athletes. In terms of sensitivity in our cohort, the timed tandem gait fell only slightly behind the K-D test as a diagnostic tool. Further investigation will determine test–retest reliability. In this cohort, we did not find SAC testing to be helpful in distinguishing the concussed athlete. A previous study of the SAC in a pediatric cohort presenting to the emergency department for concussion also did not find a significant difference in scores vs nonconcussed controls (31). Baseline SAC scores in youth populations can be very low, as observed in our study, making it difficult to find a decrement in SAC scores after concussion in certain athletes. Similar to the timed tandem gait, SAC testing requires further validation in youth population.

REFERENCES


Retinal Ganglion Cell Layer Analysis by Optical Coherence Tomography in Toxic and Nutritional Optic Neuropathy

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Objective: To analyze the retinal ganglion cell layer (RGL) by optical coherence tomography (OCT) in toxic and nutritional optic neuropathy and to correlate its thickness and volume with functional damage.

Methods: We conducted an observational cross-sectional study in healthy subjects and in patients with toxic optic neuropathy observed in the Neuro-Ophthalmology Department of Central Lisbon Hospital Center. Complete ophthalmologic examination, OCT (Heidelberg Spectralis), and automated static perimetry were performed. Thickness and macular volume of RGL layer and inner plexiform layer were measured after manual segmentation.

Results: The study included 16 eyes of 12 healthy subjects and 16 eyes of 8 patients with toxic and nutritional optic neuropathy. Age and gender did not differ between the 2 groups. Ethambutol was the cause of toxic optic neuropathy in 4 patients and nutritional factors (tobacco–alcohol) in 4 patients. A statistically significant decrease in thickness and volume of RGL, in all quadrants at 2 and 3 mm, was detected in individuals with optic neuropathy compared with controls (P < 0.01). A positive correlation between RGL thickness and mean deviation (MD) and between RGL volume and MD was detected (P < 0.05). There was a negative correlation between MD and time of disease (r = 0.846 P = 0.001) and a positive correlation between MD and visual acuity in logMAR (r = 0.739 P = 0.006). A majority of the structural parameters also correlated negatively with time of disease (P < 0.05).

Conclusions: Decreased RGL thickness and volume detected in this study support a mechanism of RGL toxicity. RGL analysis may contribute to the diagnosis and management of toxic and nutritional optic neuropathies.

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Toxic and nutritional optic neuropathies (TNON) are characterized by bilateral, progressive, and painless vision loss (1). Ganglion cell toxicity has been proposed as a pathophysiologic mechanism in these optic neuropathies, although the precise mechanism remains poorly understood (2–5).

Typical patients with TNON develop central or cecocentral scotomas, and color vision and contrast sensitivity are impaired (1, 2, 4, 6). Early in the clinical course, the optic discs appear normal, and additional testing may be required to establish the correct diagnosis. In TNON, retinal nerve fiber layer (RNFL) thinning measured by optical coherence tomography (OCT) can be helpful in detecting disease before fundus changes appear. Thinning of the RNFL begins in the inferotemporal sector of the papillomacular bundle and involves all quadrants in later stages (2, 7–9) but not before vision loss (10–12). Retinal ganglion cell layer (RGL) analysis by spectral domain OCT (SD-OCT) has been described in a variety of optic neuropathies, including...
glaucoma (13–18), optic neuritis (19, 20), nonarteritic ischemic optic neuropathy (21, 22), papilledema due to idiopathic intracranial hypertension (23), and Leber hereditary optic neuropathy (24).

The purpose of our study was to analyze RGL layer by SD-OCT in patients with TNON and correlate its thickness and volume with functional damage.

METHODS

Participant Selection

A prospective, observational cross-sectional study was performed on all patients with TNON in our Neuro-Ophthalmology Department from August 1, 2012 to July 31, 2013. Age- and sex-matched healthy controls were selected from the General Ophthalmology Department of the Central Lisbon Hospital Center. The diagnosis of TNON was established by a neuro-ophthalmologist after obtaining a careful history and excluding other causes of optic neuropathy including Leber hereditary optic neuropathy (negativity for the 3 major mitochondrial DNA mutations: 11778 G>A, 3460 G>A, and 14484T>C), autosomal dominant optic atrophy, inflammatory optic neuropathy, ischemic optic neuropathy, compressive optic neuropathy, and glaucoma. Patients were excluded with concomitant ocular or neurological disease and with refractive error ± 4 diopters. Based on self-reporting and analysis of medical records, we documented the time and onset of TNON.

Causative factors of the optic neuropathy were ethambutol (4 patients) and poor nutrition (alcohol–tobacco) (4 patients). Ethambutol was prescribed for pulmonary (3 patients) and renal (1 patient) tuberculosis. The regimen of 2 patients was 2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol followed by 4 months of isoniazid and ethambutol (2HRZE/6HE), 1 patient 3 times weekly and 1 daily. The regimen of the other 2 patients with isoniazid resistance was 6 months of rifampicin, pyrazinamide, and ethambutol (daily) (6RZE). Ethambutol dosage was 20 mg/kg on daily regimen and 35 mg/kg on 3 times weekly regimen. The first 2 patients were diagnosed during the continuation phase of treatment (fifth and seventh months) and the other 2 after the end of the treatment (1 and 2 months after completion). Patients with nutritional optic neuropathy had a long history of heavy tobacco use (30, 58, 44, and 75 pack-years) and alcohol consumption (252, 174, 286, 56 g daily for 13, 16, 14, and 30 years, respectively). One patient had low levels of vitamin B12 and folate, and the others had normal values. Two patients had high serum lactate levels.

Controls were healthy individuals based on the criteria of 20/20 visual acuity (VA) and no history of ocular, neurologic, or systemic disease.

Procedures

All participants underwent full ophthalmologic examination, SD-OCT (Heidelberg Engineering, Heidelberg, Germany), and automated static perimetry (ASP) using Octopus 900 (Haag-Streit, Switzerland). VA was calculated in logMAR. RGL segmentation was performed manually by transferring the points of the 2 boarding lines of the retina obtained automatically to RGL borders. Three to 9 points were needed to define the borders, depending on the boundary curvature. This segmentation, centered on the fovea, was performed in 25 horizontal scans with 6.1-mm length separated by 250 μm. The macular thickness (in micrometers) and volume (in cubic micrometers) of RGL (RGL and inner plexiform layer) were then obtained automatically, in a circular area centered on the fovea with 2 and 3 mm diameters, in superior (S), temporal (T), inferior (I), and nasal (N) quadrants (Fig. 1). ASP was acquired with Octopus strategy G2 and analyzed as mean deviation (MD in decibel).

Two patients with TNON did not have reliable ASP results and were excluded from the analysis.

SD-OCT and ASP were evaluated offline by 1 masked observer.

Macular thickness and volume of RGL of the TNON group were compared with those of the control group. In the TNON group, macular thickness and volume of RGL, MD, VA, and time of disease were correlated.

Statistics

Statistical analysis was conducted using SPSS Statistics version 20.0. Mean and SD were calculated. Groups were compared using Mann–Whitney or χ² tests. Spearman correlation was used to correlate TNON group variables. P values less than 0.05 were considered statistically significant.

Ethics Statement

The study followed the tenets of the Declaration of Helsinki, and written informed consent was obtained from all participants.

RESULTS

Clinical data of patients with TNON and controls are summarized in Table 1. Statistically significant differences were detected in VA and MD of the ASP.

A statistically significant decrease in the thickness and volume of RGL, in all quadrants at 2 and 3 mm, was detected in the optic neuropathy group compared with controls (P < 0.01). A greater decrease was detected in inferior thickness and volume at 2 mm and in nasal thickness and volume at 3 mm (see Supplemental Digital Content, Table E1, http://links.lww.com/WNO/A142).

A positive correlation (P < 0.05) between RGL thickness and MD and between RGL volume and MD was detected (see Supplemental Digital Content, Table E2,
A negative correlation between MD and time of disease ($r = 0.846\, P = 0.0001$) and a positive correlation between MD and VA in logMAR ($r = 0.739\, P = 0.006$) was also obtained (see Supplemental Digital Content, Table E2, http://links.lww.com/WNO/A143, and Fig E3, http://links.lww.com/WNO/A139).

The majority of the structural parameters also correlated negatively with time of disease ($P < 0.05$) (see Supplemental Digital Content, Table E3, http://links.lww.com/WNO/A144, Figs E4 and E5, http://links.lww.com/WNO/A140 and http://links.lww.com/WNO/A141).

**DISCUSSION**

Observer-dependent RGL analysis by manual segmentation has been validated by Wang et al (13). Using this method, our study detected decreased RGL thickness and volume in patients with TNON, supporting the premise that these optic neuropathies are primarily due to injury of the RGLs (2–4).

In the TNON group, MD decrease (MD values are positive with Octopus perimetry) correlated with VA increase and time of disease progression, which corroborates what has been reported in the literature (8, 12). With greater time of disease, there was a decrease in the thickness and volume of RGL, which, in conjunction to MD decrease and VA increase, raises questions about the functionality of the ganglion cells in the acute phase and at the end of toxic exposure. The greatest decrease in RGL thickness and volume of RGL layer occurred in the inferonasal quadrants, supporting early papillomacular bundle impairment in its inferotemporal sector (2, 8). This is consistent with histopathology studies (5,7).

A genetic predisposition of increased mitochondrial oxidative stress may be associated with TNON (25), and the pattern of RNFL and RGL loss seems similar to other mitochondrial optic neuropathies including Leber hereditary optic neuropathy (22, 26) and dominant optic atrophy (27, 28). Our study was limited by a small number of patients.

**FIG. 1.** RGL manual segmentation in a control patient. Thickness and volume by quadrants are shown in areas of 2 mm and 3 mm diameter. RGL, retinal ganglion cell layer.

**TABLE 1.** Clinical features of patients with TNON and controls

<table>
<thead>
<tr>
<th></th>
<th>TNON</th>
<th>Controls</th>
<th>$P$ value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (eyes/patients)</td>
<td>16/8</td>
<td>16/12</td>
<td></td>
</tr>
<tr>
<td>Etiology (neutral/toxic)</td>
<td>4/4</td>
<td>7/5</td>
<td>0.264</td>
</tr>
<tr>
<td>Gender (F/M)</td>
<td>4/4</td>
<td>7/5</td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>66.0 ± 21.1</td>
<td>58.2 ± 9.3</td>
<td>0.851</td>
</tr>
<tr>
<td>VA (logMAR)</td>
<td>0.82 ± 0.41</td>
<td>0.0 ± 0.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MD (dB)</td>
<td>−8.48 ± 6.88</td>
<td>0.47 ± 1.10</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Mann–Whitney/$\chi^2$.  
F, female; M, male.
REFERENCES

Diagnostic Algorithm for Patients With Suspected Giant Cell Arteritis

Mays A. El-Dairi, MD, Lan Chang, MD, Alan D. Proia, MD, PhD, Thomas J. Cummings, MD, Sandra S. Stinnett, DrPH, M. Tariq Bhatti, MD

Background: To identify clinical and laboratory factors contributing to the diagnosis of giant cell arteritis (GCA) and develop a diagnostic algorithm for the evaluation of GCA.

Methods: Retrospective review of 213 consecutive cases of temporal artery biopsy (TAB) seen at a single academic center over a 10-year period (2000–2009). Pathologic specimens were re-reviewed and agreement between the original and second readings was assessed. A composite clinical suspicion score was created by adding 1 point for each of the following criteria: anterior extracranial circulation ischemia, new onset headache, abnormal laboratory results (erythrocyte sedimentation rate, C-reactive protein (CRP), or platelet count), jaw claudication, abnormal or tender superficial temporal artery, constitutional symptoms, and polymyalgia rheumatica; one point was subtracted if a comorbid condition could explain a criterion.

Results: Of the 204 TABs analyzed, pathologic findings were confirmatory in 49 (24.0%) and suggestive in 12 (5.9%). TAB-positive patients were more likely to be older (age 75.2 ± 7.8 vs 69.7 ± 11.0 years, P = 0.0002), complain of jaw claudication (relative-risk = 3.26, P = 0.0014), and have thrombocytosis (relative-risk = 3.3, P = 0.0072) and elevated CRP (relative-risk = 1.8, P = 0.037). None of the patients with a clinical score less than 2 had a positive TAB. Diabetes mellitus and kidney disease were often the explanation for the symptoms and abnormal clinical finding(s) that led to a negative TAB.

Conclusions: We propose a clinical algorithm that is highly predictive for a positive TAB and can be valuable in the evaluation process of suspected cases of GCA.

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Giant cell arteritis (GCA), also known as temporal or cranial arteritis, is the most common primary vasculitis of the elderly in the Western world (1). The prevalence among whites older than 50 years is 10–25/100,000 (1,2). Multisystem involvement is often the case, affecting the ocular and cerebral circulations. Because of the variability and sometimes paucity of disease manifestations, the clinical diagnosis can be challenging, yet critical, in preventing the devastating complications of visual loss (3,4) and neurological deficits (3).

GCA affects medium- to large-sized arteries, with a preferential effect on branches of the internal and external carotid arteries (5). Blindness and stroke are feared complications because of inflammation-induced vascular occlusion (5). Headache, the most common symptom in patients with GCA, is believed to be due to inflammation of branches of the external carotid artery (6), and jaw claudication, which has been shown to be a specific symptom of GCA, is a consequence of ischemia to the masseter muscle supplied by the maxillary artery (7,8).

In 1990, the American College of Rheumatology (ACR) published a 5-point scoring system for diagnosing GCA that was initially developed for research purposes. A score of 3 or more had a sensitivity of 93.5% and specificity of 91.2% in distinguishing GCA from other vasculitides (9,10). With these criteria, it is possible to make the diagnosis of GCA without a temporal artery biopsy (TAB) (11). However, most experts recommend a TAB when GCA is suspected because the results of a TAB significantly increase the agreement between the clinical diagnosis and the ACR criteria (12,13).
The goal of our study was to discern clinical and laboratory findings that may improve the diagnostic yield of a positive TAB. We compiled and reviewed our 10-year experience at Duke University Medical Center and performed a review of the clinical studies published in the English literature to derive an algorithm that would be useful in determining the risk for GCA before obtaining a TAB.

**METHODS**

The Institutional Review Board at Duke University Medical Center approved this retrospective study. The Department of Pathology electronic database (Cerner PathNet, North Kansas City, MO) was used to identify all patients who underwent a TAB at Duke University Medical Center from 2000 to 2009. Corresponding electronic and paper medical records were reviewed to gather clinical, demographic, pathologic, and laboratory information. Coexisting ocular and medical conditions were collected. Visual acuity measurements at presentation and at the last eye examination were recorded and the surgical specialty obtaining the TAB, length of the TAB specimen, and number of days on corticosteroid before the time of the TAB.

All TABs processed at Duke University Medical Center were cut into 6 to 10 cross sections, depending on the vessel length, and then the cross sections were prepared as ten slides containing 5 μm histological sections of every cross section. Each slide represented a “level” or “step section” with 50 μm between slides. Thus, 500 μm of each of the multiple artery cross sections was evaluated to minimize the possibility of a skip lesion being missed during histological evaluation. Seven slides were stained with hematoxylin and eosin, 1 slide with elastic stain to evaluate the internal elastic lamina, 1 slide with Masson trichrome stain to highlight scarring, and 1 slide with Congo red to evaluate for amyloid deposition.

Three inflammatory markers were measured: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and platelet count. Three methods were used to identify the upper limits of normal for the ESR:

1. ESR > 50 as per ACR criteria
2. The formula of Miller et al (14):
   - Male: age/2.
   - Female: (age + 10)/2.
3. The formula of Hayreh et al (15):
   - Male: 17.3 + (0.18 × age).
   - Female: 22.1 + (0.18 × age).

We defined an elevated CRP as >0.5 mg/dL and an elevated platelet count as >400,000/μL.

The association between symptoms or laboratory findings and a positive/healed TAB was determined by using contingency tables and chi-square analyses. Statistical significance was defined as $P \leq 0.05$. Equivocal biopsies were excluded from the pathological analysis. Risk factors meeting statistical significance and odds ratios were tabulated.

With the aim of creating a numerical score that would improve the sensitivity of a TAB, 2 score models were created:

1. Composite score for clinical suspicion calculated by adding 1 point for each item on the following list: 1) new onset headache, 2) scalp tenderness or abnormal superficial temporal artery (STA) on examination, 3) elevation of any inflammatory marker (ESR, CRP, or platelet count), 4) evidence of new onset clinical ischemia involving the anterior extracranial vasculature, 5) jaw claudication, and 6) signs and symptoms consistent with polymyalgia rheumatica (PMR). One point was subtracted for each sign or symptom that could be explained by an alternative condition (e.g., poorly controlled diabetes mellitus and evidence of ischemia, kidney disease, chronic rheumatologic condition, or central retinal artery occlusion in the setting of carotid artery occlusion).

2. A weighted score for clinical suspicion was created by the addition of each statistically significant variable tested multiplied by its own relative risk (RR).

An area under the receiver operating curve (ROC) was created for each of the above scores, and the sensitivity and specificity were calculated.

The TAB pathology report was reviewed, and slides from all cases were re-reviewed in a masked fashion by one of the authors (A.D.P.) (see Supplemental Digital Content, Figure E1, http://links.lww.com/WNO/A145). Positive TABs were labeled as active or healed arteritis. Active GCA was defined as inflammation comprising lymphocytes, epithelioid histiocytes, occasional giant cells, and disruption/loss of the internal elastic lamina (16,17). Healed arteritis was identified and distinguished from age-related change by diffuse and marked intimal thickening, large areas of absent internal elastic lamina, asymmetric (eccentric) atrophy and fibrosis of the tunica media, adventitial or transmural scarring, and sometimes vascularization of the media or residual foci of lymphocytes (17,18). The presence of chronic perivascular inflammation adjacent to the STA was considered to be of no clinical significance when this was the sole abnormality in the biopsy sections (19). In a minority of cases, we could not distinguish healed arteritis from senescent changes, (18) and these were classified as suggestive TABs. Negative TAB exhibited a normal histological appearance and lacked any of the above histopathological findings (18).

**RESULTS**

Two hundred thirteen consecutive TABs were identified. Nine TABs were excluded from analysis for the following reasons: 4 did not yield the STA, 3 were inadequate specimens, 1 was performed at an outside institution and...
the original slides could not be retrieved for review. One biopsy was excluded because it was performed as part of a parotidectomy for a parotid tumor (the result of that biopsy was positive, but prebiopsy clinical and laboratory information was not available). A total of 204 TABs were analyzed. Forty-nine cases (24.0%) exhibited active or healed GCA (mean age, 74.8 ± 7.8 years), and 12 cases (5.9%) were suggestive of GCA (mean age 76.7 ± 6.5 years). One hundred and forty-three (70.0%) patients had a negative TAB (mean age 69.7 ± 11.0 years). Patients older than 65 years were more likely to have a positive TAB than those younger than 65 years (RR = 3.05, P = 0.0002). The youngest patient with a positive TAB was 54 years old (Table 1).

Among the 143 patients with a negative TAB, the most common final diagnoses were primary headache (17.8%) and an autoimmune disease other than GCA or PMR (8.5%). The remaining alternative diagnoses are detailed in Table 2. One patient had a TAB consistent with Takayasu arteritis. Patients with diabetes mellitus and kidney disease (creatinine >2.0 mg/dL or estimated glomerular filtration rate <30 mL/min) were less likely to have a positive TAB (RR = 0.331, P = 0.0007 and RR = 0.286, P = 0.0141, respectively).

Thirty-three patients with negative TAB would have met ACR criteria for GCA. Five patients were given the diagnosis of TAB-negative GCA; of these, 2 had bilateral TABs. All 5 of these patients had ESR >60 mm/h, 2 patients had jaw claudication, 1 patient had bilateral choroidal ischemia, 1 patient had double vision, 1 patient had constitutional symptoms, and 3 patients had headaches. In all patients, the symptoms improved with the institution of oral corticosteroids.

Twelve patients had a TAB that was considered suspicious for GCA. Three were not given the clinical diagnosis of GCA because another cause was identified (aortic hematoma, musculoskeletal headache, and age-related macular degeneration). Of the remaining 9 patients who were ultimately diagnosed with GCA, 2 of them had an optic neuropathy, 5 had headaches, 3 had jaw claudication, 1 had malaise, 1 had fever, and 4 had an elevated ESR.

Of the 49 patients with positive TAB, the 3 most common findings on presentation were headache (38/47), vision change (16/46), and elevated ESR (33/46). Of the 9 (18.4%) patients who did not complain of headaches, 2 had scalp tenderness, 6 had vision loss, 1 had PMR without vision loss, two had constitutional symptoms, and all had elevated ESR. Of the patients who had vision loss, 9 (56.2%) presented with vision of less than 20/100. Only 1 patient presented with bilateral visual loss.

The clinical sign that had the highest likelihood for positive TAB was jaw claudication (RR = 3.26; P = 0.0014). Isolated findings of headache, scalp tenderness, fever, weight loss, visual loss, and ischemia were not associated with a positive TAB (Table 1).

The majority (74.5%) of TABs were performed on females; however, there was no statistical difference in TAB outcome between men and women. Out of 52 African American patients who underwent TAB, 3 had a positive TAB and 2 had a suggestive TAB (RR for whites vs African Americans was 4.61; P = 0.0013; OR = 6.59). No Hispanic or Asian patients underwent a TAB during the study period. One patient from the Arabian Peninsula had a negative TAB. Race was not recorded in 4 patients with a negative TAB.

The laboratory marker with the strongest association with positive TAB was an elevated platelet count greater than 400,000/µL (RR = 3.3; P = 0.0072) (Table 2). Elevated CRP had a RR of 1.8 (P = 0.037). ESR (>50 mm/h) or an elevated ESR after adjustment according to either the Hayreh or Miller formulas was not associated with a positive TAB (P > 0.18). When both ESR and CRP were elevated, the value was 0.067. It should be noted that only 37.8% (77/204) subjects had a CRP before the TAB. When both ESR and platelet counts were elevated, RR was 2.01 (P = 0.017). Having any isolated laboratory value elevated, ESR, CRP, or platelet count was not associated with a positive TAB; however, when 2 or more inflammatory markers were elevated, the RR was 3.4 (P < 0.0001) (23/25 patients with elevated platelet count also had a high ESR, and 63/76 patients with a high CRP also had high ESR). An increase in ESR, CRP, and platelet count was present in 11 of 77 patients (14.7%) and was not associated with positive TAB. Two patients with positive TAB had normal ESR, CRP, and platelet counts.

The majority of TABs were performed by the ophthalmology service (136/204 [68%]) followed by otolaryngology (57/204 [28%]). Neurosurgery, vascular surgery, and general surgery were the other services that performed a TAB. The length of the STA did not vary greatly among the different subspecialties. The average length was 20.8 mm.

Seven sequential and 5 simultaneous TABs were performed. In 2 patients (16.6%), there was a discordant pathologic diagnosis. Upon re-review of the original slides, the first biopsy in one of the 2 cases (performed at an outside institution) was believed to be positive, making the discordance rate 8.3%.

Thirty-two patients with a positive TAB and 10 patients with suspicious TAB were on corticosteroid therapy before the TAB. Ten patients with a positive TAB had been on the steroids for more than 3 weeks, and 8 of them had been on the steroids for more than 2 months. Two patients with positive TAB had been on steroids for more than 1 year (Table 1).

A longer segment biopsy was not associated with a higher rate of positive TAB (mean biopsy length 21.6 ± 4.1 for a negative TAB vs 21.6 ± 6.8, P = 0.49 for a positive TAB, P = 0.49).

Both score models had a very high association with a positive or suspicious TAB (P < 0.001). For the
### TABLE 1.
Temporal artery biopsy results with respect to demographics, symptoms, laboratory findings, clinical suspicion, and steroid treatment before biopsy

<table>
<thead>
<tr>
<th>Condition</th>
<th>Positive TAB (N = 49)</th>
<th>Suggestive TAB (N = 12)</th>
<th>Negative TAB (N = 143)</th>
<th>Relative Risk</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Temporal artery biopsy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temporal arteritis (2)</td>
<td>23/49 (48.7)</td>
<td>12/12 (100.0)</td>
<td>0/89 (0.0)</td>
<td>1.88</td>
<td>1.01</td>
</tr>
<tr>
<td>Temporal arteritis (1)</td>
<td>7/12 (58.3)</td>
<td>6/12 (50.0)</td>
<td>6/12 (50.0)</td>
<td>1.3</td>
<td>1.01</td>
</tr>
<tr>
<td>Temporal arteritis (0)</td>
<td>0/12 (0.0)</td>
<td>0/12 (0.0)</td>
<td>74/121 (61.1)</td>
<td>1.01</td>
<td>1.01</td>
</tr>
<tr>
<td><strong>Relative Risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Constitutional symptoms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>16/54 (29.6)</td>
<td>3/54 (5.6)</td>
<td>123/54 (23.2)</td>
<td>1.01</td>
<td>1.01</td>
</tr>
<tr>
<td><strong>Laboratory findings</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any abnormal laboratory result (ESR &gt; 50 mm/h, CRP &gt; 0.5 mg/dl)</td>
<td>33/137 (24.4)</td>
<td>8/137 (6.0)</td>
<td>92/137 (68.2)</td>
<td>1.01</td>
<td>1.01</td>
</tr>
<tr>
<td><strong>Relative Risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Clinical suspicion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMR</td>
<td>3/15 (20.0)</td>
<td>1/15 (6.7)</td>
<td>11/15 (73.3)</td>
<td>1.01</td>
<td>1.01</td>
</tr>
<tr>
<td><strong>Jaw claudication</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evidence of anterior extracranial ischemia</td>
<td>16/54 (29.6)</td>
<td>3/54 (5.6)</td>
<td>123/54 (23.2)</td>
<td>1.01</td>
<td>1.01</td>
</tr>
<tr>
<td><strong>Relative Risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Evidence of anterior extracranial ischemia</strong></td>
<td>16/54 (29.6)</td>
<td>3/54 (5.6)</td>
<td>123/54 (23.2)</td>
<td>1.01</td>
<td>1.01</td>
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<tr>
<td><strong>Relative Risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prior corticosteroid treatment in days (range)</strong></td>
<td>48.7 (2 d to 3 yr)</td>
<td>12.1 (0 – 30 d)</td>
<td>17.7 (1 d to 1 yr)</td>
<td>1.01</td>
<td>1.01</td>
</tr>
</tbody>
</table>

*Seven anterior ischemic optic neuropathy, 4 transient vision loss, 4 retinal artery occlusion, 2 posterior ischemic optic neuropathy, 2 diplopia, 2 complained of decreased vision loss but no documented ophthalmic examination found. Eleven patients had no evidence of vision loss on follow-up examination.

PMR, polymyalgia rheumatica; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.


Original Contribution

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TABLE 2. Final diagnoses when temporal artery biopsy was normal

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of Patients</th>
<th>Percentage</th>
<th>List of Final Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary headache syndrome</td>
<td>26</td>
<td>17.8</td>
<td>Worsening glaucoma, age-related macular degeneration, enlarging cavernous sinus aneurysm, known rheumatologic disease, known chronic infection, polio neuropathy, cancer</td>
</tr>
<tr>
<td>Symptoms could have been explained by patient’s chronic condition</td>
<td>15</td>
<td>10.3</td>
<td>Unidentified connective tissue disease, granulomatosis with polyangitis, Takayasu arteritis, Crohn disease, rheumatoid arthritis, systemic lupus erythematosus, optic neuritis, vitreoretinitis, Hashimoto thyroiditis, central centrifugal cicatricial alopecia</td>
</tr>
<tr>
<td>Autoimmune disease other than GCA</td>
<td>12</td>
<td>8.2</td>
<td>Syphilis, meningitis, cervical facet osteoarthritis, hepatitis C, facial cellulitis, mycobacterium avium acellularis, ethmoid sinusitis, severe skin back infection, urinary tract infection</td>
</tr>
<tr>
<td>Infection</td>
<td>11</td>
<td>7.5</td>
<td>Vitreoretinitis, elevated intraocular pressure, corneal abrasion, blepharitis, skin nodule</td>
</tr>
<tr>
<td>Polymyalgia rheumatica</td>
<td>9</td>
<td>6.2</td>
<td>Carotid artery disease, progressive angina, hypertension, hypotension</td>
</tr>
<tr>
<td>Symptoms resolved with no sequelae</td>
<td>8</td>
<td>5.5</td>
<td>Amiodarone optic neuropathy, metformin myopathy, statin myopathy, cocaine vasculopathy</td>
</tr>
<tr>
<td>Nonarteritic anterior ischemic optic neuropathy</td>
<td>6</td>
<td>4.1</td>
<td>Vitreoretinitis, elevated intraocular pressure, corneal abrasion, blepharitis, skin nodule</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>6</td>
<td>4.1</td>
<td>Vitreoretinitis, elevated intraocular pressure, corneal abrasion, blepharitis, skin nodule</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>6</td>
<td>4.1</td>
<td>Vitreoretinitis, elevated intraocular pressure, corneal abrasion, blepharitis, skin nodule</td>
</tr>
<tr>
<td>Symptoms explained after ophthalmalic examination</td>
<td>5</td>
<td>3.4</td>
<td>Vitreoretinitis, elevated intraocular pressure, corneal abrasion, blepharitis, skin nodule</td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>4</td>
<td>2.7</td>
<td>Vitreoretinitis, elevated intraocular pressure, corneal abrasion, blepharitis, skin nodule</td>
</tr>
<tr>
<td>Biopsy-negative giant cell arteritis</td>
<td>5</td>
<td>3.4</td>
<td>Vitreoretinitis, elevated intraocular pressure, corneal abrasion, blepharitis, skin nodule</td>
</tr>
<tr>
<td>Total number of negative biopsies</td>
<td>143</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GCA, giant cell arteritis.

nonweighted score, ROC was 0.8. Patients with a score of 1 (only 1 criterion suggestive of GCA) had 0% rate of a positive TAB (70 patients), those with a score of 2 had a 32.9% chance of a positive TAB (26/79), those with a score of 3 or higher had a 55.6% chance of a positive TAB (30/54) (score 3 = 19/39 [49%], score 4 = 6/9 [67%], score 5 = 5/7 [71.4%]), and with a score of 5 had biopsy negative GCA. None of our patients had more than 5 of these criteria.

For the weighted score, the formula was 3.05 (if age >65 years) + 4.61 (if race = white) + 3.26 (if jaw claudication present) + 1.8 (if CRP higher than 0.5 mg/dL) + 3.3 (if platelets >400,000/L) + 3.4 (if >2 laboratory results abnormal). ROC for the weighted score was 0.77. A cut-point score of 8.5 had a positive predictive value of 0.82 and a negative predictive value of 0.53 for a positive TAB.

DISCUSSION

In our series, the yield of a positive or healed TAB was 24%, consistent with the previously published data ranging from 13.7% to 38.4% (5,6,8,20–24). Based on a comprehensive analysis of the demographic, clinical, and laboratory data of all the patients in this study, we developed an algorithm to quantitate the risk of GCA and increase the likelihood of positive TAB (Fig. 1). Given the potentially devastating visual and systemic complications associated with GCA and the relatively few surgical complications associated with a TAB, the low yield of a positive TAB seems justified in patients suspected of having GCA. However, the relatively low yield of obtaining a positive TAB indicates a deficiency in the ability of the clinician to reliably ascertain whether a patient has GCA based on clinical and laboratory findings. At this time, alternative diagnostic tools, such as Doppler ultrasonography and magnetic resonance imaging, cannot reliably replace a TAB (25).

Although some have supported use of ACR criteria to diagnose GCA, (10,12), the rate of a negative TAB in patients meeting the ACR criteria has ranged from 15% to 39% (12,16,26). In our study, 21% of TAB-negative patients met at least 3 of the ACR criteria. In one series, while all GCA patients with a positive TAB met at least 3 ACR criteria, there were 68.5% of the negative TAB patients who also met at least 3 of the ACR criteria (27). Conversely, Murchison et al (12) reported that 25.7% of their patients with a positive TAB would not have met the
ACR criteria. All of our patients who had an ultimate diagnosis of GCA met at least 3 of the ACR criteria.

A TAB is considered the gold standard for confirming the diagnosing of GCA. A TAB is 100% specific for GCA but is not 100% sensitive (20,28). Niederkohr and Levin (28) estimated the sensitivity of a single TAB to be 87.1%. We found the sensitivity of a positive TAB was 91.4%, similar to the rate reported in the literature (29).

In our study, the most common mimickers of GCA were primary headache syndrome, PMR, and chronic disease (diabetes mellitus and renal failure). Rheumatologic diseases (rheumatoid arthritis, systemic lupus erythematosus), lymphoma, and vasculopathy also have been reported to mimic GCA (21). Similar to the results reported by Matthews et al (30), we found that patients with diabetes and kidney disease were less likely to have a positive TAB. This does not imply that patients with diabetes or kidney disease are protected from GCA, but clinicians should keep in mind that diabetes and kidney disease have vascular complications that may mimic GCA.

Among our patients with a positive TAB, the most common presenting symptoms were headaches and vision loss. A new onset severe headache has been reported in approximately 2/3 of patients with GCA (15). Vision loss, one of the most feared complications of GCA, has been reported in 14%–70% of cases (3,31). Among our patients, 42.3% complained of vision changes and of those, 50% had permanent vision loss in 1 or both eyes due to retinal or

**FIG. 1.** Algorithm to determine prebiopsy risk for giant cell arteritis. TAB, temporal artery biopsy; GCA, giant cell arteritis; AION, anterior ischemic optic neuropathy; PION, posterior ischemic optic neuropathy; CRAO, central retinal artery occlusion; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.
optic nerve ischemia. In our case series, the rate of permanent vision loss was 21.2% (Table 1).

Among our patients, the most common abnormal laboratory measure was an elevated platelet count, followed by a high CRP. Elevation of these 2 inflammatory markers was highly predictive of a positive TAB, similar to previously reported laboratory findings in GCA (22,23). Although an increase in any 2 laboratory markers was associated with a higher risk for a positive TAB, an increase in all 3 was not associated with a positive TAB. This is contrary to previously published studies (22,23), and we suspect the reason for this finding is that only about one-third of our patients had all three markers measured before TAB. Also, in concordance with previous studies (15,24), jaw claudication was associated with the greatest likelihood of GCA while none of the other symptoms (e.g., headache, vision loss, abnormal STA, PMR) were predictive of GCA as isolated markers.

In most cases, a unilateral TAB is often sufficient in suspected cases of GCA (32,33), but in 3%-5% of cases, there can be significant differences in the pathologic grade of disease from one side to the other in cases of bilateral TAB (30,31). The majority of our patients had a unilateral TAB, but of those patients who had a bilateral biopsy, the discordance rate was 8.3%. In an analysis of 11 pooled studies, Niederkohr and Levin (34) found the mean discordance rate for bilateral TAB to be 5.5%. Our discordance rate is higher than previously published studies, but our sample size of bilateral TAB was small. Based on our study and the low discordant rate published in the literature, we believe that a unilateral TAB is sufficient to exclude the diagnosis of GCA in patients for which there is a low clinical suspicion (33). Even with a high concordance in pathologic diagnosis, a statistically significant difference can also be observed in the objective histopathologic severity scale between the 2 sides (35). The single patient in our study with a discordant result on bilateral TABs was likely due to the inadequate sampling on the initial TAB (9-mm segment), although we cannot exclude the possibility of misinterpreting the first specimen (the histopathologic slides were not available for our review).

Although corticosteroid use decreases the inflammatory change in the vessel wall, it does not have an effect on scarring of the vascular media and surrounding the inner elastic lamina, thereby permitting a pathologic diagnosis (36,37). Even in patients who developed GCA with a history of PMR and chronic low-dose corticosteroid use, TAB remained positive in 88% of cases in one study (26). Two of our patients who had been on chronic steroid therapy for more than 1 year had a positive TAB.

We combined the results of our study with a review of the current literature to modify the algorithm published by Shmerling (38) for evaluating and treating suspected GCA (Fig. 1). The first step in the algorithm is to assess how many clinical and laboratory findings are consistent with GCA, which will determine the degree of clinical suspicion. If a patient meets less than 2 clinical or laboratory criteria, the likelihood of GCA is very low. If a patient meets 2 criteria, the likelihood of GCA is moderate (33%), and if a patient achieves 3 criteria, the likelihood is high (56%).

We recognize the limitations of our studies. Being a retrospective study, medical records reviewed may have had incomplete documentation of symptoms, signs, and laboratory results. A number of patients were not tested for CRP and platelet count, and the clinical examination of the STA was not always documented. Intravenous fluorescein angiography was performed on only 7 of the patients in our study. We were not able to assess the prevalence of choroidal ischemia and the sensitivity of this test in predicting a positive TAB. Also, some patients did not undergo a follow-up ophthalmologic examination at our medical center and, as a result, we were unable to assess the risk of vision loss after low-dose or high-dose corticosteroid treatment. Given the relatively low prevalence of GCA, a multicentered prospective study with various ethnic representations would be necessary for controlling these limitations.

REFERENCES

Correlation Between Structural and Functional Retinal Changes in Parkinson Disease

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Background: To evaluate structural changes in the retina and correlate those with visual function measurements in patients with Parkinson disease (PD).

Methods: A cross-sectional comparative study of 20 patients with PD and 20 age-matched healthy controls was conducted. Visual acuity, color vision, contrast sensitivity, visual fields, pattern-evoked response (VER), and multifocal electoretinogram were recorded to determine functional change, whereas structural changes were evaluated with retinal nerve fiber layer (RNFL) thickness, macular thickness, macular volume, and ganglion cell–inner plexiform layer complex (GCL-IPL) thickness using spectral domain ocular coherence tomography (SD-OCT).

Results: PD patients ranged from Stage 1–3, with median Stage 2 (Hoehn and Yahr Classification) with mean Unified Parkinson Disease Rating Scale III score of 19 ± 10.42, and average disease duration of 5.8 ± 2.78 years. Visual acuity, color vision, and visual fields were unaffected but contrast sensitivity was significantly worse than controls \( (P < 0.001) \). Multifocal electoretinogram values in the central 2° field revealed decreased foveal electrical activity, with increased pattern VER amplitude and latency. Significant RNFL thinning was observed in the average RNFL \( (P = 0.033) \), superior \( (P = 0.018) \), and temporal \( (P = 0.036) \) quadrants. Significant ganglion cell layer loss was captured on SD-OCT with average, minimum GCL-IPL, and all 6 sectors showing thinning \( (P \leq 0.003) \). The functional changes correlated significantly with structural changes, disease duration, and severity. There was no correlation between structural changes in the retina and disease duration or severity.

Conclusions: Subclinical visual dysfunction was observed in patients with PD with good structural–functional correlation. GCL-IPL thinning may be a more reliable parameter than RNFL thickness for structural alterations of the retina in patients with PD.

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Parkinson disease (PD) is a progressive motor disorder associated with the degeneration of dopaminergic neurons in the basal ganglia substantia nigra pars compacta region of the mid brain, with increasing prevalence of the disease with aging. It is primarily characterized by motor manifestations, such as resting tremor, rigidity, and bradykinesia, although nonmotor involvement such as that of the visual system is also seen.

Dopamine, besides its major involvement in motor function, has also been fully established as a neurotransmitter and modulator in the retina, specifically in the inner nuclear layer and inner plexiform layers (1). These dopaminergic neurons in the retina modulate the receptive field of ganglion cells to partially control visual functions including spatial contrast sensitivity and color vision, which are often impaired in PD (1,2).

Optical coherence tomography (OCT) has been used to demonstrate structural changes in the peripapillary retinal nerve fiber layer (RNFL) in some patients in PD (3–7). Visual dysfunction has been documented in PD; multifocal electroretinogram (mERG) testing has demonstrated decreased electrical activity at the fovea (8). However, it is as yet unclear whether the functional loss is concurrent with the structural damage in the retina.

This study evaluated the relationship between structure and function in patients with PD.

METHODS

We conducted a cross-sectional comparative study at a tertiary care center for ophthalmology and neurology,
after prior approval from the registered institutional ethics committee and in compliance with the tenets of the Declaration of Helsinki.

Patients were recruited from the neurology outpatient department who met the study criteria. Sample size was calculated to detect a difference of 10 µm in average RNFL thickness, with a power of 90% and confidence interval (CI) of 95% (9). The required sample size was 20 patients in each group.

The study group consisted of individuals with known idiopathic PD (diagnosed on the basis of United Kingdom Parkinson Disease Society Brain Bank clinical diagnostic criteria) and twenty age-matched healthy controls with no systemic or ocular disease (10). Disease duration was based on the patients’ recollection of onset of symptoms. Both eyes of all patients were included in concordance with a previous recommendation in literature resulting from an observed interocular asymmetry in PD (11). Patients with coexisting neurodegenerative disorders or an ocular disease likely to demonstrate OCT changes or preclude accurate examination, and those unwilling or unable to cooperate for examination were excluded from the study. Informed consent was obtained from all study participants.

All enrolled patients underwent a detailed history, ocular and neurological examinations, and investigations to evaluate visual function. Severity of disease was assessed by Modified Hoehn and Yahr (H&Y) Scale and Unified Parkinson Disease Rating Scale III (UPDRS-III) (12,13).

Each eye was subjected to each testing modality. Best-corrected visual acuity was recorded on the Snellen chart under standard illumination. Color vision was assessed using Ishihara pseudoisochromatic test plates, and contrast sensitivity was measured by the Pelli–Robson chart. Pattern visual-evoked response (VER) was recorded using the Nicolet Ganzfeld 2015 visual stimulator and monitor (Nicolet Biomedical, Madison, WI). Monocular whole-field stimulation with a checkerboard pattern (reversal time of 500 milliseconds) was used, and all the patients were tested from a distance of 1 m. Pattern VER records the electrical activity of the visual cortex created by stimulation of the retina and is useful in measuring optic nerve function and monitor macular pathway. Pattern VER amplitude and latency were analyzed. Visual fields were recorded by the automated Visual Field Analysers 750i (Carl Zeiss Meditec Inc, Dublin, CA) 30-2 SITA Standard strategy, and kinetic perimetry (Haag-Streit AG, Kôniz, Switzerland) was performed in patients with twice unreliable automated visual fields. Visual field results were considered reliable if the false-positive and false-negative responses were lower than 33% and fixation losses lower than 20%. Multifocal electrotetarnogram was recorded using MetroVision monitor system. Multifocal ERG produces topographical maps of retinal function and measures the photoreceptor integrity and post-receptor activity. The root mean square (RMS) signal and waveform in the central 2° zone was analyzed. The RMS analysis characterizes the energy content of each response. S/Sp is the ratio between RMS value in a given zone and RMS value of periphery. The typical waveform of the basic mfERG response is a biphasic wave with an initial negative deflection followed by a positive peak. There is a second negative deflection after the positive peak. These 3 peaks are called N1, P1, and N2, respectively. N1/Np and P1/Pp signify the ratio of the amplitude of these waves in a given zone to the amplitude of these waves in periphery. P1/N1 signifies the ratio of the amplitude of the P1 wave to the amplitude of the N1 wave in a given zone.

Spectral domain optical coherence tomography (SD-OCT) was done using Cirrus HD-OCT Model 4000 (Carl Zeiss Meditec Inc, Dublin, CA) and was used to assess RNFL thickness using an Optic Disc Cube 200 × 200 scan. Average RNFL thickness was analyzed in 4 quadrants. Macular volume was assessed using a Macular Cube 512 × 128 scan, and a high-definition crosshair scan was also acquired, with each high-definition scan composed of 1024 A-scans. Ganglion cell analysis algorithm was used to analyze the ganglion cell–inner plexiform layer complex (GCL-IPL) separately. GCL-IPL was analyzed according to 6 sectors, in addition to average and minimum thickness values.

Statistical analysis was carried out using Stata 11.0 (College Station, TX). Data were presented as median (range) or mean ± SD as appropriate. The visual acuity, contrast sensitivity, multifocal ERG, pattern VER, RNFL thickness, GCL-IPL thickness, macular thickness, and volume were compared between the 2 groups using generalized estimating equation because these values were measured from both the eyes and the controls were age-matched with the cases, which made the data correlated. The correlation of structural and functional changes in retina with each other and with disease duration and severity were evaluated using Spearman rank calculation coefficient. The P value less than 0.05 was considered significant.

RESULTS

Twenty patients (40 eyes) with PD and 20 (40 eyes) age-matched healthy controls were examined. The mean age of individuals with PD was 58.6 ± 9.5 years (range, 37–73 years) and of controls was 58.4 ± 9.3 years (range, 37–73 years). The severity of disease was 2 (median) with a range of 1–3 (Modified Hoehn & Yahr Scale). The mean UPDRS-III score was 19 ± 10.4 (range, 7–51). The average duration of the disease was 5.8 ± 2.8 years (range, 2–10 years).

The median best-corrected visual acuity in cases was 20/20 (range, 20/20 to 20/32); and in controls, it was 20/20 (range, 20/20 to 20/32) with a P value of 0.481. The anterior segment, intraocular pressure, and fundus appearance were within normal limits in both cases and controls. Color vision was within normal limits in all the patients. The contrast sensitivity was significantly decreased in
patients with PD (1.46 ± 0.11) as compared with controls (1.56 ± 0.07) with a P value <0.001 (difference 0.19 [95% CI, 0.04–0.15]). Visual fields were found to be normal in all cases and controls. Nine patients with PD had unreliable visual fields despite twice repeating the test. In these cases, kinetic visual fields were performed and were within normal limits. One control with unreliable automated visual fields had normal kinetic visual fields.

A generalized decrease in retinal electrical activity was observed on mfERG in our patient cohort. Multifocal ERG values were analyzed in the central 2° field, representing the foveal electrical activity. RMS signal, S/Sp ratio, (ratio of RMS value in central 2° and RMS value in periphery), amplitudes (in nanovolts) of N1 and P1 waves were decreased, and P1 and N2 wave implicit times were prolonged in patients with PD. There was no difference in N1 wave implicit time (in milliseconds), N2 wave amplitude, and P1/N1 ratio between cases and controls (Supplemental Digital Content, Table E1).

The pattern VER average amplitude was 9.4 ± 2.3 μV in patients with PD and 8.3 ± 1.6 μV in controls (P value: 0.036; difference 1.15 [95% CI, 0.1–2.2]). The pattern VER latency was also increased and was 110.2 ± 8.6 milliseconds and 105 ± 3.1 milliseconds in controls (P value: 0.015; difference 5.15 [95% CI, 1.0–9.3]).

Significant RNFL thinning was found in our patients in superior (P value: 0.018) and temporal (P value: 0.036) quadrants, with the average RNFL (P value: 0.033) also being thinner than normal age-matched controls. There was no difference in nasal and inferior quadrants between patients and controls (Supplemental Digital Content, Table E2).

The GC-IPL complex was significantly thinner in cases of PD in all 6 sectors. The average and minimum GCL-IPL values were also decreased in cases compared with controls (P value ≤0.001) (Supplemental Digital Content, Table E3).

There was no difference in average macular thickness (patients: 269.2 ± 17.2 μm; controls: 273.1 ± 10.9; P = 0.3; difference −3.9 [95% CI, −11.3 to 3.5]), central macular thickness (cases: 241.7 ± 31.8; controls: 247.1 ± 17.7; P = 0.2; difference −5.4 [95% CI −14.0 to 3.3]) and macular volume (cases: 9.7 ± 0.6 μm³; controls: 9.8 ± 0.4 μm³; P = 0.4; difference −0.1 [95% CI −0.3 to 0.2]).

The structural and functional changes in the retina were correlated with the disease duration and severity and were also correlated with each other. A significant correlation was observed between the functional changes in retina (pattern VER latency, RMS signal, and P1 wave amplitude) and both disease duration and severity. The structural changes on OCT (RNFL and GCL-IPL thickness) did not significantly correlate with either disease duration or severity, except for an inverse correlation between UPDRS-III score and average RNFL thickness. A weak but significant correlation was also observed between structural changes on OCT (RNFL and GCL-IPL thickness) and functional changes on mfERG (RMS signal and P1 wave amplitude). Pattern VER latency correlated significantly with RNFL thickness but not with GCL-IPL thickness (Supplemental Digital Content, Table E4).

**DISCUSSION**

In our study, patients with PD had normal visual acuity, color vision, and visual fields, although significant contrast sensitivity abnormalities were observed. Previous reports have documented declining visual acuity with increasing disease severity, yet our results do not support this finding, possibly because of the relatively early stage of disease of recruited patients (14). Contrast sensitivity was shown to be a more sensitive parameter (15,16) of visual function, and this was the only visual functional abnormality detected.

Our patients had normal visual fields. In cases where automated fields were unreliable, a manual kinetic perimetry demonstrated normal results. Keeping in mind the conflicting reports in literature regarding visual field changes in patients with PD, it is likely that fields remain preserved at least in the mild-to-moderate stages of the disease (3,8,17). Pattern VER amplitude and latency were increased in cases of PD. All patients with PD were on dopaminergic drugs, and this might explain the increase in pattern VER amplitude (18). Increased pattern VER latency signifies electrophysiological dysfunction in patients with PD, which has been demonstrated in earlier studies using VEP and pattern ERG (19–22). Pattern VER latency is less likely to be affected by dopaminergic drugs and seems to be a more sensitive measure of foveal electrical activity than pattern VER amplitude. Multifocal ERG in central 2° revealed reduced foveal activity in patients with PD. Only 1 previous study used mfERG in cases of PD with similar results (8). We are unaware of any reports on the effect of dopaminergic drugs on multifocal ERG in patients with PD. VEP measures the integrity of the entire visual pathway, whereas multifocal ERG is specific for local retinal function, and this may in part explain the decreased amplitude observed in mfERG despite dopaminergic treatment. The decreased foveal electrical activity and abnormal contrast sensitivity in the presence of normal visual acuity may be used to detect early subclinical visual functional impairment in PD.

RNFL thickness analysis revealed thinning in the superior, temporal, and inferior quadrants of patients with PD compared with controls. The effect of PD on structural aspects of the retina has led to reports with conflicting results (3,8,9,23). However, a recent meta-analysis has shown a generalized RNFL thinning in all quadrants (5). The RNFL represents axons of the ganglion cells and impoverished dopaminergic input to the ganglion cells, which leads to atrophy of these selected fibers, which reflects as
RNFL thinning (1,2,24). In addition, we postulate that glutamate and neurotrophin deprivation in PD can activate ganglion cell apoptosis, which may explain the GC-IPL thinning noted in our study (2,24). We used the Cirrus HD-OCT ganglion cell analysis algorithm, which can automatically segment macular GCL-IPL and measure GCL-IPL thickness with excellent intervisit reproducibility (25).

Previous studies have evaluated ganglion cell layer or inner retinal layers using different segmentation algorithms with similar results (26,27).

Disease duration and severity correlated with electrophysiological changes in the retina of patients with PD. With increasing duration and severity of the disease, there was increased pattern VER latency and decreased foveal electrical activity on mfERG. Increasing severity of structural alterations on OCT, detected by RNFL and GCL-IPL thinning were related to decrease in foveal electrical activity. This suggests some degree of structural–functional correlation although the patient may have only subclinical visual dysfunction in the form of impaired contrast sensitivity. There was no clear relationship between the duration and severity of disease with structural changes on OCT. Only the UPDRS-III score was inversely correlated with RNFL thickness, possibly because our patients were in mild-to-moderate stages of disease. Earlier studies attempting to correlate disease duration and severity with retinal changes have shown variable results (4,28,29).

The small sample size and inability to include advanced stages of PD were limitations of our study. The pathological changes in PD are expected to increase with increasing severity of the disease. Our lack of patients with advanced PD (Stages 4 and 5) may have been a factor in our inability to correlate disease severity with structural alterations on SD-OCT.

In conclusion, contrast sensitivity and mfERG were found to be sensitive indicators of visual dysfunction, whereas the ganglion cell layer-inner plexiform layer analysis was a sensitive indicator of structural alterations in patients with PD. There is a subclinical visual dysfunction even in early stages of PD, which correlates with structural changes in the retina.

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Difficulties in Daily Life Reported by Patients With Homonymous Visual Field Defects

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Background: Homonymous visual field defects (HVFD) are common after postchiasmatic acquired brain injury and may have a significant impact on independent living and participation in society. Vision-related difficulties experienced in daily life are usually assessed using questionnaires. The current study 1) links the content of 3 of these questionnaires to the International Classification of Functioning, Disability and Health (ICF) and 2) provides analyses of vision-related difficulties reported by patients with HVFD and minimal comorbidities.

Methods: Fifty-four patients with homonymous hemianopia or quadrantanopia were asked about difficulties experienced in daily life because of their HVFD. This was performed during a structured interview including 3 standardized questionnaires: National Eye Institute Visual Functioning Questionnaire, Independent Mobility Questionnaire, and Cerebral Visual Disorders Questionnaire. The reported difficulties were linked to the ICF according to the ICF linking rules. Main outcome measures were presence or absence of experienced difficulties.

Results: The ICF linking procedure resulted in a classification table that can be used in future studies of vision-related difficulties. Besides well-known difficulties related to reading, orientation, and mobility, a high proportion of patients with HVFD reported problems that previously have not been documented in the literature, such as impaired light sensitivity, color vision, and perception of depth.

Conclusions: A systematic inventory of difficulties experienced in daily life by patients with HVFD was performed using the ICF. These findings have implications for future study, assessment and rehabilitation of patients with HVFD.

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It has been estimated that homonymous visual field defects (HVFD) occur in 89% of patients with acquired postchiasmatic brain damage (1). The most common form of HVFD is homonymous hemianopia. Estimated percentages of homonymous hemianopia among stroke patients range from 8% to 31% (2,3). HVFD can have far-reaching negative effects on both general and vision-related quality of life (4–6). HVFD has been mainly associated with difficulties in reading, orientation, and mobility (1,5,7–11). De Haan et al (12) pointed out that only a small percentage of studies on HVFD have focused on the consequences of HVFD on daily activities and participation in society.

In this study, a systematic inventory was performed on the difficulties experienced in daily life by patients with HVFD. Although several studies have reported on a number of difficulties caused by HVFD, the results were not based on systematic exploration, or resulted from very small patient groups or patients with other physical impairments. In our study, patients with HVFD had minimal comorbidities and to minimize bias from previous studies or clinical experience, a predefined classification system (International Classification of Functioning, Disability and Health; ICF) was used. A better understanding of the difficulties experienced in daily life by patients with HVFD hopefully will lead to better assessment and treatment methods.

METHODS

Participants

Patients were recruited from Royal Dutch Visio and Bartiméus, the 2 largest centers for rehabilitation for blind and partially sighted people in the Netherlands. Between

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

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2010 and 2012, 373 patients suspected of having HVFD applied for rehabilitation at these institutes. Patients were subjected to extensive and standardized ophthalmologic and neuropsychological testing. In order to be included in the study, a HVFD was required. Time since origin of the field defect had to exceed 5 months, minimizing chances for spontaneous recovery of the field defect. Patients were excluded if visual acuity was \( \geq 20/40 \) or if they had impaired ocular motility. Further exclusion criteria were symptoms of neglect, memory problems, depression, anxiety disorder, mini-mental state examination score <24 or disorders of visual perception including visual spatial perception, visual object recognition, visual attention, or visuconstruction.

Fifty-four patients met inclusion criteria and consisted of 35 men and 19 women with a mean age of 56 years (range, 27–75 years). In 37 patients, the HVFD was left-sided and 17 right-sided. The field defects existed for 20 months on average (range, 5–122 months). Eleven patients had a quadrantanopia (10 left-sided and 1 right-sided), whereas the remaining 43 cases had a hemianopia. Causes of the HVFD were ischemic stroke (n = 39), hemorrhagic stroke (n = 6), traumatic brain injury (n = 3), penetrating head trauma (n = 1), tumor resection (n = 1), extirpation of arteriovenous malformation with post-operative hemorrhage (n = 1), or combined etiology (n = 3).

All patients provided written informed consent. The Medical Research Ethics Committee of the University Medical Center Groningen approved the study. The study was performed in accordance with the 2008 Declaration of Helsinki.

**Procedure and Materials**
Patients were examined individually during a structured interview. The assessment began with an open-ended request to name the difficulties they experienced in daily life because of their HVFD. Next, the effect of the HVFD on an extensive set of different situations was assessed using 3 standardized questionnaires. The Visual Functioning Questionnaire (NEI-VFQ-25) (13) consists of multiple choice questions concerning the influence of visual impairment on several health-related domains, including emotional well-being, social functioning, and tasks related to daily visual functioning. With the Independent Mobility Questionnaire (IMQ) (14), the perceived ability for independent mobility despite visual impairment is evaluated. Patients rated on 5-point scales the amount of difficulty they experience in 35 mobility situations. In the second portion of the IMQ, the respondent is asked about mobility-related behavior, such as falling, use of mobility aids, and medication usage. The first part of the Cerebral Visual Disorders (CVD) questionnaire consists of 9 questions to assess the presence or absence of vision-related problems (15). In the second part, respondents are asked to indicate on 5-point scales how much difficulty is experienced with 12 particular activities (16). The CVD contains questions not only on mobility and reading but also on other vision-related problems, such as perception of depth and colors, light sensitivity, and visual hallucinations. The combination of these questionnaires enables extensive examination of a wide range of functions, activities, and participation. Since reading difficulties are common in patients with HVFD, the questionnaires were administered in oral interviews.

**Step 1: Analysis of Reported Difficulties**
The process of conversion and analysis are listed in Supplemental Digital Content, Table E1, http://links.lww.com/WNO/A151.

Linking the reported difficulties to the ICF: Since the 3 questionnaires in total contained 102 questions, categorization of the items of these questionnaires, as well as the answers to the open-ended questions, was necessary for an accessible overview of the reported difficulties. Several methods for categorizing items or concepts have been used previously. Such classifications were often based on face validity or common sense and sometimes descriptions of how categories were constructed were completely missing. Although these methods can be very effective to answer certain research questions, they can easily be subject to bias.

To keep an unbiased objective approach in evaluating the reported difficulties, we applied a predefined classification system as a reference framework. The ICF (17), as developed by the World Health Organization, has been used in numerous studies (12,18–20). In the ICF, concepts related to the health are categorized in body functions and structures, activities and participation, as well as environmental factors and personal factors. These components are further structured in domains and categories, resulting in unique codes for individual concepts.

In our study, 3 investigators working in the field of visual perception and familiar with the ICF model independently determined the concepts included in the questions and answers. Each concept was linked to the most precise ICF code according to the guidelines by Cieza et al (21) using the digital ICF browser (http://apps.who.int/classifications/icfbrowser). When comparisons of the 3 classifications revealed differences, an attempt was made to reach consensus. If this failed, a fourth evaluator was involved.

**Spontaneously Reported Difficulties**
The spontaneously reported problems on open-ended questions were grouped by ICF code. For every ICF code, the number of patients reporting at least 1 problem in this area was calculated.

**Standardized Questionnaires**
Because the answer formats of the questionnaire items differed markedly, the different scales were converted into dichotomous scales. The cut-points for the dichotomous scales were based on the conversion rule that every answer stronger than “sometimes a problem” (or words with similar...
inclination, such as “a little difficulty”) was classified as “difficulty present” (see Supplemental Digital Content, Table E2, http://links.lww.com/WNO/A152). The items were then grouped by ICF code. Within every ICF code, the number of patients indicating at least one of the problems to be present was determined.

**Step 2: In-Depth Analysis**

After determining the number of patients reporting difficulties within the various ICF categories, a more in-depth examination was performed for problems that appear less directly related to missing part of the visual field. In this analysis, the effect of age on the presence or absence of a reported difficulty was assessed (2-tailed independent samples T-tests). Only results with a P-value <0.5 were reported.

**RESULTS**

**Step 1: Analysis of Reported Difficulties**

Linking the reported difficulties to the ICF: Classifying the reported difficulties according to the ICF linking rules (1) resulted in 268 concepts for the open-ended question and 248 concepts for the standardized questionnaires. During the process of linking these concepts, in 4 of 516 concepts, no unanimous decision was reached, and the fourth evaluator was involved in the decision process, resulting in agreement (see Supplemental Digital Content, Table E3, http://links.lww.com/WNO/A153).

Eighty-seven concepts were found not to be covered by the ICF. In order to include these in the analysis, they were grouped based on common sense, resulting in a number of additional categories (see Supplemental Digital Content, Table E3, http://links.lww.com/WNO/A153). For the answers on the open-ended question, these additional categories were difficulties seeing objects or people in time due to incomplete visual overview, difficulty using the computer, misplacing or knocking over of objects on tables, difficulty choosing suitable positions when sitting together with a group, falling or catching oneself, being easily overstimulated, and bumping the head.

**Spontaneously Reported Difficulties**

Among the frequently reported problems were difficulties seeing objects or people in time resulting from incomplete visual overview, as well as problems with orientation, way finding, and mobility (walking around obstacles or people, cycling or driving a car). Reading problems included finding the beginning of the next line or limited endurance. Other activities often experienced as problematic were placing or avoiding knocking over objects on tables, difficulty choosing suitable positions when sitting together with a group, falling or catching oneself, being easily overstimulated, and bumping the head.

**Light Sensitivity**

The majority of patients (94%) rated at least 1 item on the function light sensitivity (h21020) or the environmental factor light intensity (e2400) as problematic. Fifty-two percent of patients reported that everything seemed darker or that more light was needed when reading. However, 54% reported that they were now more blinded by bright lights. It frustrated, irritable, insecure, scared, or tense) because of their visual disorder. Environmental factors frequently reported to cause difficulties were unfamiliar surroundings, crowded areas, darkness, or inclement weather.

Patients spontaneously reported several activities to be problematic that were not in the questionnaires. These included use of a computer (n = 10), riding a bicycle (n = 7), placing or avoiding knocking over objects (n = 6), writing (n = 3), cooking (n = 2), doing housework (n = 1), and following conversations (when sitting at an unfavorable position at a table; n = 2). Patients reported increased fatigability (n = 7), difficulty multitasking (n = 2), and trouble seeing contrasts (n = 1).

**Standardized Questionnaires**

Table E3 (see Supplemental Digital Content, http://links.lww.com/WNO/A153) shows the number of patients who reported problems per ICF category. The results confirm the findings of previous studies that patients with HVFD experience difficulty with finding objects, reading, and mobility. HVFD had a significant impact on participating in society, as the majority of patients reported difficulty with recreation and leisure activities, such as participation in sports, arts and culture, hobbies, and social events.

The ICF specifies 9 domains within the level of activities and participation. On average, patients reported difficulties in 5 (range 2–8) different domains. The number of domains affected was correlated negatively with age (r = 0.38, P = 0.005). Younger patients reported difficulties in more domains than older patients. Time since onset of the HVFD was neither related to age (r = 0.14, P = 0.312) nor to the number of domains in which difficulties were experienced (r = 0.23, P = 0.099). On average, women experienced difficulties in more domains of activities and participation than men (t(52) = 3.20, P = 0.002, mean difference 1.1 domain). Neither side of field defect (t(52) = 1.32, P = 0.191) nor type of field defect (hemianopia vs quadrantanopia; t(52) = 0.01, P = 0.992) was significantly related to the number of domains affected. Comparisons for gender, side of field defect, and type of field defect should be interpreted with caution because of uneven sample sizes.

**Step 2: In-Depth Analysis**

It was more problematic to link some repeated problems to missing a portion of the visual field. These were analyzed in more depth.
appeared that 30% of patients experienced both of these problems concurrently. Walking in high glare areas was rated as problematic in 75% of cases, whereas 80% experienced problems walking, driving, or going down steps in dimly lit or dark areas. Combining all questions related to light sensitivity showed that 76% patients experienced problems with bright lights or high glare areas, as well as having increased difficulty seeing in dimly lit or dark areas. Difficulty adjusting to changes in light intensity, for example, when moving from indoor to outdoor, was reported by 56% of patients.

Color Vision
Twenty-one percent of patients responded to the question on color vision (b21021) that colors did not seem as bright as before their HVFD.

Perception of Depth
One patient elaborated on the open-ended question that perception of depth, distance, and velocity were disturbed. When all patients were asked whether they experienced problems estimating the height of the next step when using stairs, 21% agreed.

Negative Feelings and Thoughts
The results revealed that HVFD in most patients entailed negative feelings and thoughts (b152). In response to the open-ended question, 35% of patients experienced feelings of insecurity in unknown or busy surroundings or during walking, cycling, or driving. As indicated by the standardized questionnaire, 74% of patients reported worrying about their eyesight at least some of the time (28% most of time, 2% all the time). Half of the patients (50%) experienced feelings of frustration about their eyesight. Worries about doing things because of their eyesight that will embarrass oneself or others were reported by 31%. Eighty-four percent reported to be irritable because difficulties with vision. Fear of falling was reported by 44%. Sixty-five percent felt unsatisfied with their current ability to travel, and these participants were significantly younger compared to the participants reporting to be satisfied with their traveling abilities ($t(50.4) = -2.341, P = 0.023$). Regarding physical sensations, 20% of the patients reported pain or discomfort in or around the eyes, preventing them to do the things they wanted to do (b220, b280).

Independence
The majority of patients reported that the HVFD restrained them in performing activities without help from others (d2102). Seventy-two percent indicated that they needed or received an increased amount of help from others because of their visual impairment. Seventy percent felt restricted in walking independently, and 44% indicated that they rarely left the house without someone to accompany them. Those that asked someone to accompany them were found to be significantly younger ($t(52) = -3.391, P = 0.001$).

DISCUSSION
We conducted a systematic inventory of the difficulties that 54 patients with HVFD experienced in daily life, expressed in terms of the ICF. To this end, 3 questionnaires often used in studies of visual impairments (NEI-VFQ-25, IMQ, and CVD) were linked to the ICF. Not surprisingly, patients reported difficulties due to deficits in their visual environment and associated feelings of frustration and insecurity. They also reported difficulties that did not seem directly related to missing portions of the visual field, such as disturbed light sensitivity, color perception, and depth perception. Conceivably, the reported difficulties were not related to HVFD specifically but might be a more general result of brain damage. Younger patients described problems in more domains and were less satisfied with their ability to travel independently, compared with older adults. This association was not explained by a confounding effect of time since onset. Possibly, younger patients performed a wider range of activities before onset of the HVFD, making the impact of this deficit more striking.

To the best of our knowledge, there are no other systematic studies of the difficulties experienced by patients with HVFD (12), although there are reports describing a more limited scope of difficulties. Most often, these have dealt with patients’ complaints of reading, orientation, and mobility-related activities (1, 5, 7–11). Our results support these findings. Previous reports have indicated that patients with HVFD experience impaired general and vision-related quality of life (4–6). We also found that patients with HVFD frequently experienced difficulties with recreation and leisure activities, negative feelings and thoughts, and a feeling of decreased independence. In contrast to our data suggesting that younger patients experience more difficulties in daily life compared with older individuals, other studies did not find an association between age and quality of life (4–6) or found poorer quality of life in older patients (22–23). There are no other reports of problems with light sensitivity, color vision, and depth perception, but our study indicates that these problems are frequently experienced by patients with HVFD.

Our aim was not to determine the precise percentage of patients reporting a certain problem but to become aware of the full range of difficulties experienced by patients with HVFD. However, we are aware of the limitations of our report. To begin with, the ICF did not include every conceivable concept. In linking all concepts addressed in the questionnaires to the ICF, 87 (17%) were not covered by the ICF, which was mainly caused by a small number of concepts encountered with high frequency. Next, to enable quantitative assessment, data were summarized as presence or absence of a problem of at least one of the items within an ICF category. By converting ordinal scales into dichotomous scales, information of the degree of difficulty was lost.

We recognize potential sources of bias affecting generalizability of the results.
The different sample sizes for men vs women, left- vs right-sided HVFD, and quadrantanopia vs hemianopia might be the result of selection bias, possibly related to the exclusion criteria regarding comorbidity. Patients with additional comorbidities, such as neglect, low visual acuity, or impaired oculomotor functioning, might experience a different range of difficulties in daily life. The reported difficulties cannot be assumed to fully generalize to patients not requesting rehabilitation. The current study was performed in the Netherlands. Other countries might provide different challenges for patients with HVFD. Another possible source of bias relates to the answers of the participants. They spontaneously reported a number of problems that were not included in the standardized questionnaires. However, participants did experience problems mentioned in the standardized questionnaires that they had not spontaneously reported. This might suggest an acquiescence bias, possibly leading to false positives on the standardized questionnaires. Nevertheless, acquiescence bias would not account for the relative differences between frequencies of reported difficulties. A final possible source of bias regarding the standardized questionnaires may have come from the fact that not every ICF category was assessed by the same number of items (see Supplemental Digital Content, Table E3, http://links.lww.com/WNO/A153).

Based on our results, recommendations can be made for professionals involved in assessment of patients with HVFD. In addition to the well-known difficulties experienced by patients with HVFD, a number of additional impairments deserve attention, including disturbed light sensitivity, color perception, and depth perception. These problems might otherwise be overlooked when assessing the patient, as they may not be spontaneously reported. It would be useful to apply both open-ended questions, as well as standardized questionnaires, to this patient population because they were found to be complementary. These recommendations may lead to more effective and appropriate counseling and rehabilitation.

STATEMENT OF AUTHORSHIP

ACKNOWLEDGMENTS
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The authors gratefully acknowledge Christina Cordes, MSc and Stefanie de Vries, MSc of the Department of Clinical and Developmental Neuropsychology at the University of Groningen, the Netherlands, for their support in linking the questionnaires to the ICF, and Frédérique Bambach, MSc for her contribution to the data collection and analyses.

REFERENCES


Vision Loss Caused by Retinal and Lateral Geniculate Nucleus Infarction in H1N1 Influenza

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Abstract: A 13-year-old girl developed encephalopathy and severe bilateral vision loss to the level of light perception within 24 hours of having fever and myalgias heralding H1N1 influenza A. Ophthalmoscopy demonstrated findings of confluent ischemic retinopathy. Brain MRI disclosed lateral geniculate body signal abnormalities indicative of hemorrhagic infarction. Despite aggressive treatment with intravenous corticosteroids, intravenous immunoglobulin, and plasmapheresis, vision did not substantially improve. This case demonstrates that H1N1 can cause simultaneous retinal and lateral geniculate body infarctions, a combination of findings not previously described in any condition. We postulate an immunologic response to the virus marked by occlusive damage to arteriolar endothelium.

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Influenza virus has been reported to cause a variety of neurologic and ophthalmologic problems (1, 2). We report a unique case of bilateral, irreversible, severe vision loss resulting from combined retinal and lateral geniculate nucleus (LGN) infarctions, believed to be an immunologic response to the virus.

CASE REPORT

A previously healthy 13-year-old girl was admitted to hospital with fever and myalgia, followed 1 day later by lethargy and vision loss. Medical history was significant for acne, for which she had been treated with doxycycline 40 mg/d intermittently starting 2 months before symptom onset. She had not received H1N1 vaccination. In the emergency department, the patient was difficult to arouse. Within 24 hours of onset, arousal level spontaneously returned to normal, but ophthalmologic examination disclosed light perception vision in both eyes and bilateral retinal ischemic whitening.

Polymerase chain reaction testing was positive for influenza A H1N1 on secretions from a nasal swab. She was treated with oseltamivir, intravenous methylprednisolone 1000 mg, and intravenous immunoglobulin 2 g/kg for a diagnosis of presumed influenza-related encephalitis.

On transfer to our hospital 6 days later, she still had light perception vision in both eyes. Pupils measured 7 mm in dim illumination and constricted to light stimuli. The rest of the ophthalmic examination was normal except that ophthalmoscopy in both eyes revealed nearly confluent and sharp-bordered ischemic retinal white patches (Fig. 1).

Optical coherence tomography demonstrated inner retinal thickening and hyperreflectivity in both eyes. The outer retinal layers were relatively spared (Fig. 2). Fluorescein angiography showed multifocal arteriolar occlusions posteriorly with minimal late leakage and no retinal vascular abnormalities in the periphery (Fig. 3).

The retinal abnormalities did not account for the severity of vision loss. Brain magnetic resonance imaging (MRI), performed 2 days after the complaint of vision loss, demonstrated symmetric T2 hyperintensities on fluid attenuated inversion recovery (FLAIR) images in the region of both LGNs and in the cerebellar vermis and dorsal midbrain. On a follow-up study performed 7 days after symptom onset, T2 gradient echo images showed hypointensities with blooming in the LGNs, indicative of hemorrhage. These lesions showed restricted diffusion,
confirming ischemia. None showed contrast enhancement (Fig. 4).

The patient was diagnosed with bilateral retinal and LGN infarctions attributed to an immune response to the H1N1 influenza virus. After 5 plasmapheresis treatments administered over 10 days, retinal whitening began to fade and the inner retinal thickening diminished. On examination 60 days after onset, visual acuity had improved minimally to finger counting in a small sliver of inferior visual field in each eye. Pupillary constriction to light remained brisk bilaterally. The optic discs were pale, and the retinal whitening disappeared. Repeat MRI 75 days from symptom onset showed resolution of FLAIR signal changes and the expected evolution of the LGN hemorrhages.

**DISCUSSION**

Our patient manifested confluent ischemic retinal whitening with discrete margins in the posterior retina of both eyes resembling Purtscher retinopathy (3). But as dramatic as these retinal findings were, they did not account for the profound vision loss, which likely resulted from bilateral LGN infarctions. The brisk pupillary responses were the key finding that the cause of vision loss was more posterior in the visual pathways. Furthermore, the peripheral retinal perfusion was intact, which should have permitted at least count fingers vision.

This extent of retinal and LGN infarction has not been previously reported in H1N1 disease (4–6) or in any other condition. Two previous cases (7, 8) of nonconfluent cotton...
wool spots in H1N1 may have represented milder versions of ischemic retinopathy. In the first patient, visual acuity normalized over several months (7); in the second patient, bilateral peripapillary cotton wool spots resolved over 3 weeks (8).

Although isolated LGN infarction has not been reported in H1N1 influenza, bilateral panthalamic lesions have been described in 9 patients (1, 4, 6, 9–14). However, in none of those cases was the LGN infarcted without involving the rest of the thalamus, and in no case was vision loss or retinal infarction described. Rather, thalamic infarction was usually associated with infarction of the brainstem, cerebellum, and cerebral white matter. When LGN infarction has occurred selectively, the setting has been systemic hypotension, extrapontine myelinolysis, preeclampsia/eclampsia, posterior reversible encephalopathy syndrome, microangiopathy, diarrheal illness, and syphilitic vasculitis (15, 16).

Why should the retina and LGN have been selectively targeted for infarction? In acute necrotizing encephalopathy (ANE), an influenza-related condition in which hemorrhages can be seen in the deep gray matter, the pathogenesis is based on breakdown of the blood–brain barrier through cytokine storm in response to virus exposure, akin to the mechanism proposed for Purtscher retinopathy (9, 10, 17). The excessive cytokine response may be mediated by the patient’s genotype, as patients with point mutations of the nuclear pore gene RANBP2 (Ran-binding protein 2) are predisposed to the development of ANE (17, 18). RANBP2 is highly expressed in metabolically neural tissue, including the photoreceptors (17). A shared autoantibody target could also explain the exclusive involvement of the retina and LGB in our patient. A patient with ANE showed antibodies directed against Ephrin type B receptor 2 (EphB2), a protein found in neurons and vascular endothelium, which has various functions including angiogenesis, neural development, and neuroplasticity (19). EphB2 is also expressed in the retina, where it helps guide the developing retinal ganglion cell axons to form the optic nerve (20).

In 2013, the H1N1 virus was included in the United States’ quadrivalent influenza vaccine, which our patient had not received. A Japanese study suggested that mass immunization decreases pediatric mortality rates from influenza infection with central nervous system signs including influenza A encephalopathy (21), but there are no studies regarding the value of vaccination in prevention of central nervous system morbidity. A novel example of severe
H1N1-related morbidity, our case should entice physicians to encourage vaccination of their patients.

FIG. 4. Axial brain magnetic resonance imaging performed 7 days after symptom onset. A. Fluid attenuated inversion recovery sequence reveals symmetric bilateral T2 hyperintensities in the lateral geniculate nuclei. B. Gradient echo image at the same level reveals hypointensity with blooming in the same locations, consistent with hemorrhage. C. Diffusion-weighted scan shows that these areas contain bright signal, suggesting restricted diffusion. D. The apparent diffusion coefficient map demonstrates corresponding areas of darkness, confirming infarction bilaterally.

REFERENCES


Damage to the Optic Radiation in Patients With Mild Traumatic Brain Injury

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Background: There are known limitations of conventional computed tomography and magnetic resonance imaging in detecting neural injury in patients with mild traumatic brain injury (TBI). Diffusion tensor imaging (DTI) provides a method to further assess cerebral injury in this patient population. We report 2 patients with mild TBI who showed injury of the optic radiation (OR) as demonstrated by DTI.

Method: Two patients who complained of visual field loss after mild TBI and 9 age-matched normal control subjects were recruited for this study. Peripheral field defects were detected with automated perimetry in both patients.

Results: Regarding the configuration of OR, the total volume of OR was decreased in the right OR of both patients compared with controls; in contrast, the left ORs were divided into 2 parts in both patients. The voxel numbers of both ORs in both patients were more than 2 standard deviations lower than that of normal control subjects. The apparent diffusion coefficient value of the right OR in patient 2 was more than 2 standard deviations higher than that of normal controls.

Conclusions: We demonstrated injury of the OR using DTI in 2 patients who showed visual field defects after mild TBI.

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METHODS

Subjects

Two patients who complained of a visual field defect after TBI and 9 age-matched normal control subjects (5 males and 4 females; mean age: 49.22 years, range: 44–56) with no history of neurologic disease were recruited for this study. All subjects provided signed informed consent, and our institutional review board approved the study protocol.

Patient 1 was a 52-year-old woman who had suffered head trauma resulting from a pedestrian car accident. The patient experienced loss of consciousness for 30 minutes and posttraumatic amnesia for 4 hours at the time of head trauma; The Glasgow Coma Scale (29) score was 15 when the patient arrived at the hospital. Patient 2 was a 56-year-old woman who had suffered head trauma resulting from a car accident. The patient...
did lose consciousness nor develop posttraumatic amnesia; the Glasgow Coma Scale score was 15 when the patient arrived at the hospital. No specific abnormality was observed on brain MRI (T1, T2, and fluid-attenuated inversion recovery images) performed at 2.5 years (patient 1) with 1 year (patient 2) after onset (Fig. 1A). Peripheral field defects were detected with automated (Humphrey) visual field testing in both patients (Fig. 1B).

FIG. 1. Testing results in 2 patients with mild traumatic brain injury. A. Axial T2 magnetic resonance imaging shows no specific abnormalities. B. Automated visual fields reveal peripheral defects in both eyes. Diffusion tensor tractography of the optic radiations in 2 patients with traumatic brain injury (C) and normal controls (D). The total volume is decreased in the right optic radiations of both patients compared with controls, and the left optic radiations are divided into 2 parts (arrows) in both patients.
TABLE 1. Diffusion tensor image parameters of patients with mild traumatic brain injury and normal control subjects

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Controls (Range of 2 SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FA R</td>
<td>0.439</td>
<td>0.471</td>
<td>0.469 (0.425–0.514)</td>
</tr>
<tr>
<td>L</td>
<td>0.452</td>
<td>0.468</td>
<td></td>
</tr>
<tr>
<td>ADC R</td>
<td>0.831</td>
<td>1.017*</td>
<td>0.902 (0.822–0.983)</td>
</tr>
<tr>
<td>L</td>
<td>0.906</td>
<td>0.972</td>
<td></td>
</tr>
<tr>
<td>Voxel number R</td>
<td>402*</td>
<td>350*</td>
<td>1378 (935–1822)</td>
</tr>
<tr>
<td>L</td>
<td>560*</td>
<td>629*</td>
<td></td>
</tr>
</tbody>
</table>

Control data are presented as mean (±SD). *More than 2 SDs of that of normal control values. L, left; R, right; SD, standard deviation.

**Diffusion Tensor Imaging**

A 6-channel head coil on a 1.5 T Philips Gyroscan Intera (Philips, Ltd, Best, the Netherlands) with single-shot echoplanar imaging was used for acquisition of DTI data. For each of the 32 noncollinear diffusion sensitizing gradients, we acquired 70 contiguous slices parallel to the anterior commissure–posterior commissure line. Imaging parameters were as follows: acquisition matrix = 96 × 96, reconstructed to matrix = 192 × 192 matrix, field of view = 240 × 240 mm², TR = 10,398 milliseconds, TE = 72 milliseconds, parallel imaging reduction factor (SENSE factor) = 2, EPI factor = 59 and b = 1,000 s/mm², NEX = 1, slice gap = 0, and a slice thickness of 2.5 mm. Fiber tracking was performed using the fiber assignment continuous tracking algorithm implemented within the DTI task card software (Philips Extended MR WorkSpace 2.6.3). Each of the DTI replications was intraregistered to the baseline “b0” images to correct for residual eddy-current image distortions and head motion effect, using a diffusion registration package (Philips Medical Systems, Best, Netherlands). For reconstruction of the OR, we set the seed ROI on the lateral geniculate nucleus on the color map, and the target ROI was placed on the bundle of OR at the posterior one-third portion between the lateral geniculate nucleus and the occipital pole (24, 27). Fiber tracking was performed using a fractional anisotropy (FA) threshold of >0.15 and a direction threshold of <27°. We measured the FA value, apparent diffusion coefficient (ADC) value, and voxel number of each OR. DTI parameter values showing more than 2 standard deviations (SDs) of that of normal control values were defined as abnormal.

**RESULTS**

Regarding the configuration of OR, the total volume of OR was decreased in the right OR of both patients compared with those of normal controls; in contrast, the left ORs were divided into 2 parts in both patients (Figs. 1C, D). A summary of the FA, ADC values, and voxel number of the OR of patients and controls is shown in Table 1. The voxel numbers of both ORs in both patients were more than 2 SDs lower than that of normal control subjects. The ADC value of the right OR in patient 2 was more than 2 SDs higher than that of normal control subjects.

**DISCUSSION**

We investigated the configuration and DTI parameters of the OR in patients who showed visual field defects after mild TBI. According to our findings, the configuration of both ORs in both patients was abnormal compared with those of normal controls. In addition, the voxel numbers of both ORs in both patients were decreased and the ADC value of the left OR in patient 2 was increased without change of FA value in both patients. FA value represents the degree of directionality of microstructures (axon, myelin, and microtubule), and ADC value indicates the magnitude of water diffusion (30). In contrast, the voxel number is determined by the number of neural fibers contained within a neural tract (31). Therefore, the decrement of tract volume of both ORs in both patients suggested decreased neural fibers of the OR. In addition, the increased ADC value of the left OR in patient 2 indicated mild injury of a neural tract or local cell death as did the finding of the left ORs dividing into 2 parts in both patients.

A number of reports using DTI have documented OR damage in patients with TBI (13, 27, 28). Kwon and Jang (27) described a patient with OR injury on DTI after epidural hematoma in the left temporoparietal lobe. The patient complained of right homonymous hemianopia, which was confirmed by automated visual field testing. Although no abnormality was found on conventional MRI, DTI demonstrated decreased fiber density along the midpoint of the left OR. FA values around the injury site were decreased and ADC values were increased compared with controls, consistent with neuronal injury. After head trauma, Yeo et al (28) reported a patient with right homonymous hemianopia and discontinuation of the left OR on DTI due to hemorrhage in the left occipital lobe after head trauma. Huang et al (13) studied a group of military and civilian patients who sustained mild TBI. Abnormalities were detected in the ORs of some of these patients but clinical findings, including visual field results, were not reported.
In conclusion, we documented injury of the ORs using DTI in 2 patients who showed visual field abnormalities after mild TBI. Our results suggest that DTI may be a useful technique in patients with mild TBI complaining of visual field loss. Further studies involving a large number of patients are needed to verify and confirm our findings.

STATEMENT OF AUTHORSHIP
Category 1: a. Conception and design: S. H. Jang; b. Acquisition of data: J. P. Seo; c. Analysis and interpretation of data: J. P. Seo.

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Nerve Fiber Layer Infarcts in Thiamine Deficiency

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Abstract: Thiamine deficiency classically manifests as the triad of Wernicke encephalopathy: acute confusional state, ataxic gait, and ocular motor dysfunction. However, most patients do not present with this classic triad. Optic neuropathy in thiamine deficiency is a rare manifestation and is usually associated with fundus appearances of optic disc swelling or optic disc pallor. We present 2 unique cases of thiamine deficiency where the fundus demonstrated peripapillary retinal nerve fiber layer thickening without florid disc swelling or pallor.

CASE 1

A 56-year-old woman reported 1 week of progressive visual loss in both eyes, preceded by 6 weeks of poor diet secondary to oral discomfort after dental extraction. She had a history of long-standing alcohol consumption of 10.7 standard drinks daily and tobacco use of 20 cigarettes a day. Examination revealed that she was malnourished with a body mass index of 15 kg/m². Visual acuity was counting fingers in each eye, pupillary reflexes were sluggish with light-near dissociation, and horizontal gaze-evoked nystagmus was present. Extraocular movements were full. Fundus examination revealed bilateral superior and inferior retinal nerve fiber layer thickening with a flame-shaped hemorrhage inferior to the left macula. There was no disc swelling or pallor (Fig. 1A). Optical coherence tomography confirmed the presence of bilateral superior and inferior RNFL thickening (Fig. 2). Automated perimetry (Humphrey 30-2) showed generalized depression in the right visual field (mean deviation [MD] –28.25 dB) and a central scotoma in the left...
field (MD $-16.94$ dB). Brain magnetic resonance imaging was unremarkable, but laboratory investigations confirmed low thiamine level of 38 nmol/L (normal: 70–200 nmol/L). She was treated with thiamine and multivitamin supplementation and she made a dramatic visual recovery, with the acuity improving within days to 20/15 in both eyes.

### CASE 2

A 20-year-old woman with a history of chronic alcoholism (30 standard drinks per day) presented with severe confusion and altered consciousness. She had full ocular motility with vertical and horizontal gaze-evoked nystagmus. Fundus

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FIG. 2. Case 1. Optical coherence tomography confirms superior and inferior retinal nerve fiber layer thickening.
examination revealed bilateral RNFL thickening superior and inferior to the disc (Fig. 1B). Further examination was precluded by her severe confusion. Computed tomographic imaging of the brain was unremarkable. She was managed with hydration, correction of electrolyte imbalances, as well as thiamine and multivitamin replacements. Her fundus findings resolved. However, she was diagnosed with Wernicke–Korsakoff syndrome and suffered ongoing cognitive impairment and short-term memory loss.

Thiamine (vitamin B1) is a water-soluble vitamin that plays a major role as a coenzyme in carbohydrate metabolism in the central nervous system. Thiamine deficiency classically manifests as the triad of Wernicke encephalopathy: acute confusional state, ataxic gait, and ocular motor dysfunction. Visual loss is uncommon in thiamine deficiency and is usually bilateral, severe, and associated with optic disc swelling (1).

Optic neuropathy is a rare manifestation of thiamine deficiency. Peripapillary RNFL thickening associated with thiamine deficiency, as in our patients, has been reported previously in cases of protracted vomiting and bariatric surgery (1, 2). The slowly progressive optic neuropathy seen in chronic alcoholism more commonly produces a clinical picture of pallor of the optic discs (2–4). The fundus findings seen in our cases bear a resemblance to those seen in methanol-induced optic neuropathy and in Leber hereditary optic neuropathy, in which mitochondrial dysfunction underlie the pathogenesis. It is postulated that mitochondrial dysfunction, as a result of thiamine deficiency, first gives rise to swelling and hemorrhage of the RNFL and subsequent optic disc swelling appears only if mitochondrial damage is severe and prolonged (2–4).

Our 2 cases demonstrate a unique manifestation of thiamine deficiency: peripapillary RNFL infarcts in the absence of florid disc swelling or pallor. Furthermore, the first case is notable in that severe visual loss with peripapillary RNFL thickening and retinal hemorrhage was the only manifestation of her thiamine deficiency. Recognition of these ophthalmoscopic findings in thiamine deficiency is important to avoid unnecessary testing, which may delay urgent treatment with thiamine supplementation.

REFERENCES
Hemorrhage Within the Optic Nerve From a Cavernous Hemangioma of the Optic Disc

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Abstract:
A 49-year-old woman with a known right optic disc cavernous hemangioma experienced pain with eye movements and worsening of a superior visual field defect. While she retained 20/20 visual acuity in each eye, findings on magnetic resonance imaging were consistent with a hemorrhage in the anterior portion of the right intraorbital optic nerve. Her visual function stabilized spontaneously. We are unaware of previous reports of hemorrhage into the optic nerve from a cavernous hemangioma of the optic disc.

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a cavernous hemangioma (Fig. 1A) and a normal left optic disc. The maculæ and peripheral retina were normal in both eyes. Automated visual field testing demonstrated a superior altitudinal defect in the right eye (Fig. 1B) while the left visual field was normal.

Fluorescein angiography showed plasma-erythrocyte separation within the hemangioma with late pooling in a cluster-like formation on the optic disc (Fig. 1C). Optical coherence tomography revealed an elevated lesion of the right optic disc containing hyporeflective oval spaces (Fig. 1D).

Orbital magnetic resonance imaging (MRI) showed changes in the anterior and midorbital portions of the right optic nerve (Fig. 2). On the T2 axial images, 2 loculated foci with fluid–fluid levels were apparent. Posterior to these foci was an area of T2 signal dropout. These findings were consistent with hemorrhage of different ages within the optic nerve with various stages of blood breakdown products.

Over the next 2 months, the patient’s vision remained stable. At her 5-month follow-up visit, she reported worsening vision in the right eye. Visual field testing showed progression of her right superior altitudinal defect, but her orbital MRI was unchanged.

In 1971, Gass (1) first described cavernous hemangioma of the optic disc. This is a rare vascular hamartoma consisting of numerous, clustered, thin-walled aneurysms, appearing like a “bunch of grapes.” On fluorescein angiography, there is a slow rate of dye perfusion within the lesion and plasma-erythrocyte separation showing a fluid level within the aneurysms (2). Plasma-erythrocyte separation occurs during the late venous phase when the fluorescein pools superiority in the plasma resulting in hyperfluorescence while erythrocytes collect inferiorly. Greater than 90% of hemorrhages due to hemangioma of the optic disc are unilateral and approximately one quarter are detected within the first 3 decades of life (2). They are more prevalent in females and can be associated with other skin and central nervous system hamartomas (2,3).

Fortunately, cavernous hemangiomas of the optic disc often are asymptomatic with preserved visual acuity and a stable clinical course (1,3–5). Visual field defects commonly reveal an enlargement of the blind spot and/or nerve fiber bundle defects (2,6). Usually they do not enlarge (2); however, there are cases of documented growth over 5–10 years (7).

Cavernous hemangiomas of the optic disc are not without complications. Cases of vitreous and retinal hemorrhage from these lesions previously have been described (2,3,7,8). In a report by Kuschner et al (7), one patient had a vitreous hemorrhage that was significant enough to require vitrectomy. In cases requiring surgery, removal of portions of the tumor has been performed to reduce the risk for significant hemorrhage (3). More typically, the vitreous hemorrhages are small but have been known to recur (2,3). In these cases, observation usually is sufficient.

There are also reports of hemorrhage from optic disc cavernous hemangiomas during pregnancy (6,9). In some instances, the cause of the hemorrhage may be from Valsalva maneuvers during labor, increasing venous congestion and enlargement of the thin-walled aneurysms in these lesions.

Our patient was recovering from gastroenteritis, during which she described multiple episodes of forceful emesis shortly before the development of eye pain. With the previous reports of Valsalva-induced hemorrhages, it seems likely that our patient’s vomiting episodes provided a similar mechanism for the development of hemorrhage, which extended into the orbital portion of the optic nerve.
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Early Diagnosis of Subclinical Interferon Alpha–Associated Optic Neuropathy Using Fluorescein Angiography

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Abstract: We report a case of a 57-year-old man who presented with decreased visual acuity in the left eye secondary to nonarteritic anterior ischemic optic neuropathy (NAION) while on therapy with interferon-α for hepatitis C. Fundus fluorescein angiography revealed late leakage of both optic discs, consistent with bilateral disease. One week later, the patient developed clinical signs and symptoms consistent with NAION in the fellow eye. Fluorescein angiography may play an important role in identifying subclinical NAION in patients taking interferon-α.

CASE REPORT

A 57-year-old man complained of vision loss in the inferior visual field of his left eye. His medical history was significant for hepatitis C complicated by cirrhosis, and his treatment included INF-α (180 mg subcutaneously every week), Tacrolimus, filgrastim, and ribavirin for 24 weeks. Review of systems was negative for headaches, jaw claudication, scalp tenderness, arthralgias, weight loss, or fatigue.

Visual acuity was 20/20, right eye and 20/200, left eye. Color vision was intact in the right eye and reduced in the left eye, but there was no relative afferent pupillary defect. Automated visual field testing showed inferior field loss, much more marked in the left eye (Fig. 1A). Ophthalmoscopy revealed a normal appearing right optic disc with a cup to disc ratio of approximately 0.3, while the left disc was swollen (Fig. 2A). Because IFN-α is known to cause a retinopathy in a high percentage of patients, a fluorescein angiogram was obtained. To our surprise, it showed late bilateral optic disc leakage (Fig. 2B).

Patient testing included erythrocyte sedimentation rate, C-reactive protein, viscosity level, cryoglobulins, and hepatitis C viral load. All studies were within normal limits. Brain and orbit magnetic resonance imaging with and without contrast were unremarkable. Given the suspicion of IFN-α–associated NAION, IFN-α was discontinued.

One week later, the patient returned complaining of decreased vision in the right eye. Visual acuity was 20/80, right eye and 20/200, left eye. There was bilateral dyschromatopsia, and visual fields showed progression of bilateral inferior field defects (Fig. 1B). Both optic discs were now swollen (Fig. 2C). The patient received a ten-day
course of oral prednisone. Five months later, visual acuity and color vision were unchanged although visual fields had worsened (Fig. 1C), and there was bilateral optic disc pallor (Fig. 2D).

DISCUSSION

The interferons are a group of glycoproteins with complex antiviral, antitumor, and antiangiogenic properties. In 1995, Purvin (9) reported the development of acute bilateral sequential vision loss, likely from NAION, in two patients receiving IFN-α for malignant neoplasm. Since then, approximately 42 unilateral or bilateral cases of IFN-α–associated optic neuropathy have been published (8,10–14). According to the World Health Organization criteria, this association is considered “possible.” Although the pathophysiology of IFN-α–associated ocular toxicity is unknown, a number of mechanisms have been proposed including vasoocclusive (15), hypotensive (10,16), and immunologic (8).

NAION is characterized by decreased visual acuity, dyschromatopsia, a relative afferent pupillary defect and a swollen optic disc. Visual fields classically show an inferior altitudinal defect. Although the pathomechanism of NAION is unknown, it is presumed to result from circulatory insufficiency or infarct within the retrolaminar portion of the optic nerve head that is supplied by the short posterior ciliary arteries (SPCA).

Fluorescein angiography in NAION typically shows delayed and incomplete disc filling, late leakage of the optic disc, and no delay in choroidal filling. The normal choroidal filling time is suggestive of a relative vascular insufficiency distal to the split-off of the paraoptic branches from the SPCA (17–19).

Initially, our patient had no symptoms or definite clinical signs of bilateral NAION. Although the absence of an RAPD is consistent with bilateral involvement, there was no dyschromatopsia or optic disc edema in the asymptomatic fellow eye. However, FA demonstrated late leakage of both optic discs consistent with bilateral optic neuropathies and explains the absence of an RAPD. Given the usefulness of FA in this case to diagnose bilateral involvement, we suggest that patients with unilateral NAION presumed secondary to IFN-α should also have an FA looking for evidence of subclinical involvement of the fellow eye. This is because bilateral simultaneous NAION, whether clinical or subclinical, is much more likely to be secondary to drug toxicity from IFN-α rather than idiopathic. In cases with unilateral NAION, the clinician often struggles to decide whether NAION is idiopathic or possibly secondary to IFN-α making the decision to recommend discontinuing this medication more difficult. However, bilateral simultaneous involvement is suggestive of a toxic effect of IFN-α and should prompt the treating physician to discontinue treatment to try to salvage vision.

Although guidelines for routine ophthalmologic screening have been established for other medications with known

![Pattern deviation](image1)

![Pattern deviation](image2)

![Pattern deviation](image3)

**FIG. 1.** Automated (Humphrey 24-2) visual fields. A. At presentation, there is evidence of inferior field loss bilaterally, more prominent in the left eye. B. One week later, there is worsening of inferior field loss bilaterally. C. Five months later, visual fields show central and inferior defects in each eye.
ocular toxicity, there is no similar consensus for screening patients who are taking IFN-α for hepatitis C. Cases of clinically unilateral NAION and asymptomatic optic disc edema in the fellow eye have been reported in patients not receiving treatment with interferon-α (20). However, our case demonstrates that a patient taking IFN-α also can have asymptomatic disc edema and FA might be an important tool for the early diagnosis of impending IFN-α-associated NAION.

FIG. 2. Funduscopy and fluorescein angiography. A. At presentation, there is mild elevation of the right optic disc superiorly while the left disc is swollen with peripapillary hemorrhages. B. In the late phase of the fluorescein angiogram, there is dye leakage of both optic discs. C. One week later, there is bilateral optic disc edema. D. Five months after presentation, both discs are mildly pale.
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Ophthalmoplegia Due to Scrub Typhus

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Abstract: Scrub typhus is an acute febrile infectious disease caused by Orientia tsutsugamushi. The illness is usually characterized by fever, rash, and lymphadenopathy, but severe cases progress to pulmonary and neurological involvement. We report a 69-year-old man who developed ptosis and ophthalmoplegia with a focal nodular lesion in the anterior cavernous sinus detected with magnetic resonance imaging. Found to have scrub typhus, the ptosis and ophthalmoplegia resolved after treatment with doxycycline.


Scrub typhus is an acute febrile illness caused by Orientia tsutsugamushi, a Rickettsia species transmitted to mammals by biting larvae of chiggers (trombiculid mites) (1). The infection can induce generalized vasculitis and lymphadenopathy featuring multiorgan involvement, including meningoencephalitis (2,3). The vasculitis caused by scrub typhus is characterized by destruction of endothelial cells and perivascular infiltration of leukocytes (4). We describe a patient with scrub typhus ophthalmoplegia due to an inflammatory lesion in the anterior cavernous sinus demonstrated by magnetic resonance imaging (MRI).

CASE REPORT

A previously healthy 69-year-old farmer was referred with a 4-day history of complete left ptosis. The patient had been hospitalized with fever, truncal rash, and an eschar on his right leg. He had received 200 mg/d doxycycline for 5 days. On the fifth day, complete ptosis developed in the left eye without pain or tenderness, which prompted the referral.

On examination, the patient was afebrile (36.4°C), blood pressure was 107/65 mm Hg, and his pulse rate was 78/min. An eschar was present on his right thigh (Fig. 1). He was alert and oriented. Visual acuity was 20/20 bilaterally, and pupils were isocoric without a relative afferent pupillary defect. The patient had a complete left ptosis, and movement of the left eye was limited in all directions (Fig. 2). Trigeminal nerve function was intact as were the remaining cranial nerves.

Routine hematological and serological tests were normal except for mild elevation in liver enzyme levels: aspartate transaminase of 45 IU/L (normal: <40 IU/L) and alanine transaminase 59 IU/IL (normal: <40 IU/L). Serum immunoglobulin G (IgG) for Orientia tsutsugamushi, measured using an indirect immunofluorescent antibody (IFA) assay was 1:10,240. Cerebrospinal fluid (CSF) analysis showed a mildly elevated protein of 50.7 mg/dL (normal: 15–45 mg/dL) without pleocytosis. His tsutsugamushi CSF IgG also was highly positive (1:2,560). Chest radiography was normal. Brain MRI revealed an enhancing nodular lesion in the anterior cavernous sinus and diffuse meningeal thickening (Fig. 3). The ptosis and ophthalmoplegia resolved after treatment with doxycycline 200 mg/d for 10 days.

FIG. 1. An eschar is present on the anteromedial surface of the right thigh.
DISCUSSION

Our patient presented with ptosis and ipsilateral ophthalmoplegia presumably due to the intracranial lesion seen on brain MRI. His clinical findings (fever, truncal rash, and eschar) and an elevated IgG titer for *Orientia tsutsugamushi* in serum and CSF allowed us to diagnose scrub typhus. Because the external ophthalmoplegia resolved completely after treatment with doxycycline, the focal neurological signs and the lesion in the cavernous sinus were caused by infection or inflammation triggered by the Rickettsia organism.

Although scrub typhus may lead to central nervous system (CNS) involvement (5), focal neurologic signs or abnormal findings documented on neuroimaging rarely have been reported (2,3). In a previous case report of scrub typhus encephalomyelitis, T2 MRI demonstrated high signals in the dorsal pons and cervical spine. The authors proposed that the brain and spinal cord lesions might be due to a postinfectious immune response and did not reflect direct infection. In another case of scrub typhus encephalitis, the patient demonstrated horizontal gaze palsy, nystagmus, and ataxia (2). Multiple patchy areas of increased signal in the basal ganglia, cerebellum, and brainstem were present on T2 MRI. It was speculated that the MRI changes were due to breakdown in the blood–brain barrier, microinfarction, and edema secondary to vasculitis. We found only 2 case reports of abnormal ocular motility as the only neurological sign of scrub typhus. Both patients had unilateral sixth nerve palsies, but brain MRIs were normal (6,7). Microinfarction caused by vasculitis was proposed as the cause of the isolated cranial neuropathies.

Scrub typhus is a public health problem in the endemic area of “Tsutsugamushi triangle,” which extends from northern Japan and far-eastern Russia in the north to northern Australia in the south and to Pakistan and Afghanistan in the west. During the Second World War, many soldiers dispatched to these areas died of the disease. Many of these individuals were studied at autopsy (8,9). Focal lesions consisting of dense clusters or microglial cells (typhus nodules) or perivascular lymphocytic cell exudates were found (8). The intracranial lesion of our patient may have been a typhus nodule or leptomeningeal congestion.

Diagram of scrub typhus traditionally is based on clinical features: an eschar, a maculopapular rash, and lymphadenopathy. An eschar, which is the single most useful diagnostic clue, usually can be found on the lower extremities, genital, or axillary regions. The centrifugal

**FIG. 2.** Left ptosis is present with limited left eye movements in all directions. The left lid is held open with tape.

**FIG. 3.** Postcontrast T1 brain magnetic resonance imaging. A. Axial scan shows an enhancing nodular lesion (arrow) in the anterior portion of the left cavernous sinus. B. Coronal view also demonstrates the left cavernous sinus lesion (arrow) and diffuse meningeal enhancement (arrowheads).
maculopapular rash, which does not involve palms and soles, is also characteristic. Recently, laboratory tests including IFA and polymerase chain reaction analysis of serum have facilitated the diagnosis of scrub typhus. IFA is particularly helpful; the positivity criterion is either 1 sample with a titer of 1:400 or greater or a fourfold increase in titer to a level of 1:200 or greater (4). Although no reference Tsutsugamushi antibody titer for IFA testing of CSF has yet been established, the strongly positive CSF assay titer in our patient provided convincing evidence that the scrub typhus infection involved the CNS. Doxycycline, rifampin, azithromycin, tetracycline, and chloramphenicol have been used to treat scrub typhus (10). Doxycycline is the drug of choice for initial treatment except in rare drug-resistant cases (11). Interestingly, neurological signs can develop later in the clinical course even during the first week of antibiotic therapy (12). Because the concentration of doxycycline in the CSF is about 20% that of serum, higher dose or long-term therapy may be required with CNS involvement.

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Positive Apraclonidine Test in Horner Syndrome Caused by Thalamic Hemorrhage

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Abstract: Reversal of anisocoria following instillation of apraclonidine 0.5% has been reported in Horner syndrome caused by lesions of the central and peripheral nervous system. The shortest documented latency between symptom onset and a positive apraclonidine test is 36 hours, occurring in a patient with a pontomedullary infarct. We present the case of a 69-year-old man with Horner syndrome due to thalamic hemorrhage in whom apraclonidine testing demonstrated reversal of anisocoria 4 days after symptom onset. This is the first reported case of a positive apraclonidine test in a Horner syndrome caused by a lesion at this site. It suggests that apraclonidine testing is useful in confirming the diagnosis within days of onset even in a lesion located at the most proximal portion of the oculosympathetic pathway.

CASE REPORT

A 69-year-old man developed sudden profound lethargy, as well as numbness and weakness of the right arm. He was taking no medications and had no known medical history. On arrival at our hospital 2 days after symptom onset, he was alert with normal vital signs. Neurologic examination disclosed right hemibody hypesthesia and reduced strength in the right arm. Muscle stretch reflexes were normal. Brain magnetic resonance imaging demonstrated acute hemorrhage in the left thalamus (Fig 1).

Ophthalmologic examination was normal apart from the findings of 2 mm of left upper lid ptosis, left lower lid (reverse) ptosis, and anisocoria. In dim illumination, pupils measured 5 mm in the right eye and 3.5 mm in the left eye (Fig. 2A) constricting to 3 and 2 mm, respectively. There was no relative afferent pupillary defect. Apraclonidine 0.5% drops were administered 4 days after the onset of symptoms. Thirty minutes after instillation, pupils measured 3.5 mm in the right eye and 5 mm in the left eye, and there was slight reduction of the left upper and lower lid ptosis (Fig. 2B).

DISCUSSION

Apraclonidine is gaining acceptance as a pharmacologic diagnostic tool to confirm Horner syndrome, particularly in patients presenting with anisocoria without other localizing signs or symptoms. It is primarily an alpha-2 agonist with weak affinity for alpha-1 receptors, which are the predominant receptors in the iris dilator muscle (5). Apraclonidine has little effect on pupils in normal eyes. However, it exerts a mydriatic effect in Horner syndrome where sympathetic denervation leads to upregulation of the alpha-1 receptors (3,4). Instillation of apraclonidine causes a reversal of anisocoria, with dilation of the sympathetically dener-vated pupil.

The overall sensitivity and specificity of 0.5% apraclonidine in the diagnosis of Horner syndrome seems to be comparable with that of topical cocaine, the traditional

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agent used in pharmacologic testing for Horner syndrome (4,6–8). In the only series to report the effect of apraclonidine on control eyes (6), mydriasis was noted in 19% and lid elevation in 45% of normal eyes, but no reversal of anisocoria was observed. In one series, cocaine administration was shown to produce anisocoria >0.5 mm in 9 of 50 normal patients as compared with 118 of 119 patients with Horner syndrome (1). There have been no reports of false positive tests with apraclonidine.

The principal reservation about the value of apraclonidine in diagnosis of Horner syndrome has been the question of whether it will be positive early enough. The delay before sufficient alpha-1 upregulation occurs to produce a positive apraclonidine test is unknown. Apraclonidine testing has been positive within 1 week of carotid artery dissection (9) and cluster headache with sinusitis (10), both due to lesions of the third-order neuron of the oculosympathetic pathway. However, in a patient with a first-order Horner syndrome due to a pontomedullary infarct, the reported interval between onset of symptoms and a positive apraclonidine test was 1.5 days (11). In our patient, apraclonidine testing was positive within 4 days of symptom onset, again suggesting that upregulation of alpha-1 receptors after denervation occurs very quickly and that apraclonidine testing is likely to be valuable even in Horner syndrome caused by a lesion in the most proximal portion of the oculosympathetic pathway.

Although Horner syndrome caused by a thalamic lesion has been confirmed with cocaine testing (12), our case is the first to report a positive apraclonidine test in this setting. The 2 cases of Horner syndrome with reversal of anisocoria after less than a week of symptom onset (this case and that of a pontomedullary infarct (11)) both had central causes. A Horner syndrome due to carotid dissection (9) tested at 4 days caused partial dilation of the affected pupil but not reversal of anisocoria. It is possible that a central lesion causes complete loss of sympathetic input and may lead to more rapid sympathetic denervation than a lesion of the second- or third-order neurons. It remains to be demonstrated how early apraclonidine will be positive in the setting of more peripheral lesions causing Horner syndrome.

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**Clinical Observation**

![FIG. 1.](image-url) T2 axial (A) and coronal (B) magnetic resonance imaging shows a left thalamic hemorrhage with vasogenic edema.

![FIG. 2.](image-url) Left Horner syndrome. A. Red-free photo reveals left upper and lower eyelid ptosis and pupillary miosis. B. Thirty minutes after instillation of 0.5 apraclonidine drops, the left pupil is now larger than the right with slight reduction in the left upper and lower lid ptosis.
Dermatomyositis-Related Nonischemic Central Retinal Vein Occlusion

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Abstract: A 25-year-old woman with dermatomyositis suffered a right central retinal vein occlusion (CRVO) with visual acuity of 20/40. Examination of the right eye showed vitreous cells, suggesting inflammation of the central retinal vein leading to a CRVO as the presumed mechanism. She was admitted to hospital, and extensive evaluation was negative. She was maintained on corticosteroids to manage her dermatomyositis. One month later, she had macular edema and elevated intraocular pressure. Both resolved with dorzolamide, timolol, and intravitreal bevacizumab, and vision returned to 20/20 in the right eye.

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Dermatomyositis (DMS) is an idiopathic inflammatory myositis with characteristic cutaneous findings. The exact mechanism is unknown but is hypothesized to be immune-mediated microangiopathic disease causing ischemia and inflammation of muscles (1, 2). DMS often presents with typical skin findings, including Gottron papules on the digits, heliotrope eruption of the eyelids, and pigment changes in light exposed areas (3). These skin findings typically precede the muscle findings, which present as symmetric, proximal myalgias, most commonly affecting the deltoids and hip flexors without muscle atrophy. Other systemic findings include interstitial lung disease (4, 5), esophageal involvement (6), cardiomyopathy (7), and malignancy (3). Ocular findings in DMS are less common. We present a patient with DMS who presented with vision loss from nonischemic central retinal vein occlusion (CRVO).

CASE REPORT

A 25-year-old woman with a history of DMS and latent tuberculosis (TB) presented with 2 weeks of painless monocular vision loss of the right eye. Eight months before, she underwent muscle biopsy after 5 months of progressive proximal muscle weakness. The biopsy established the diagnosis of DMS. The patient did not have any skin findings, which likely contributed to the delay in diagnosis. Before starting corticosteroids, a cutaneous purified protein derivative test was positive, but a chest x-ray was negative. The patient had no pulmonary symptoms. For presumed latent TB, she was treated with isoniazid (INH) and pyridoxine for 9 months. For her DMS, she was prescribed prednisone 80 mg daily and slowly tapered to 17.5 mg and 15 mg on alternate days. She had no other medical illnesses, had no history of surgery, and was taking no other medications. She had no known drug allergies. She had worked as a teacher but was unemployed. She denied any history of smoking, drinking, or recreational drugs. Family history and review of systems were noncontributory.

After 8 months of steroid therapy, the patient awoke with decreased vision in the right eye. On examination, her right fundus showed diffuse intraretinal hemorrhages and optic disc and macular edema. Brain magnetic resonance imaging was normal, and she was referred for neuro-ophthalmic evaluation. Visual acuity was 20/40, right eye and 20/20, left eye. Color vision was slightly reduced in the right eye (10/11 Ishihara plates) and normal in the left eye (11/11 plates). Pupils were 5 mm in the dark to 3 mm in the light with a right relative afferent pupillary defect.
Ocular movements were intact, and alignment was orthotropic. Visual fields were full to confrontation. Slit-lamp examination was normal with intraocular pressure (IOP) of 13 mm Hg, right eye and 17 mm Hg, left eye. Funduscopy of the right eye showed disc edema, macular edema, dilated retinal vessels, and retinal hemorrhages in all 4 quadrants as well as vitreous cells (Fig. 1). The left fundus was normal.

The patient was diagnosed with a right CRVO secondary to DMS and admitted to the hospital. Complete blood count showed a normal white blood cell count, mild anemia, and a normal platelet count. C-reactive protein, anticardiolipin antibodies, antinuclear antibodies, cytoplasmic and perinuclear antineutrophilic cytoplasmic antibodies and angiotensin-converting enzyme were negative. Quantiferon gold testing for TB, syphilis serology, HIV, lysozyme, and urine histoplasma tests were all negative. Lumbar puncture revealed an elevated opening pressure of 27.5 cm H2O with protein 25 mg/dL (normal: 15–45 mg/dL), glucose 42 mg/dL (normal: 50–80 mg/dL), 1 WBC/μL, 3 RBCs/μL, cytology negative for malignancy, and negative acid-fast bacillus stain and culture.

At one-month follow-up, the patient’s right visual acuity had declined to 20/50. Her funduscopic examination showed the evolution of CRVO with retinal hemorrhages and macular edema (Fig. 2). Because her IOP was 36 mm Hg, right eye and 30 mm Hg, left eye, she was treated with dorzolamide and timolol. Intravitreal bevacizumab was injected in the right eye 3 times over the subsequent 2 months. At 3-month follow-up, her vision had improved to 20/20 in the right eye, and her IOP was 13 mm Hg, right eye and 15 mm Hg, left eye. Her right fundus showed resolving scattered intraretinal hemorrhages and improvement of macular edema.

DISCUSSION

Complement-mediated microvasculopathy is the primary hypothesized mechanism for DMS (2, 8). Systemic small-vessel vasculitis involving nearly every major organ system, but particularly of the skin and lungs, has been reported in DMS (4, 5). Ocular involvement in DMS is less common. Case reports have documented retinopathy (9–11) ocular myositis (12), frosted branch angiitis (13), and optic neuropathy (14). Fong and Schatz (15) conducted a review of CRVO in adults younger than 50 years and found that they were less likely to be associated with systemic atherosclerotic disease and more likely to be inflammatory in nature compared with older patients.

Nonischemic CRVO has been reported as a sequel of a number of autoimmune and autoimmune diseases, including sarcoidosis (16), systemic lupus erythematosus (17), Crohn disease (18), ulcerative colitis (19), and post-streptococcal uveitis syndrome (20). In DMS, an autoantibody–mediated complement activation results in destruction of the small capillary beds (8). The resulting ischemic damage of the vasculature leads to chronic inflammatory changes that occlude the vessels causing myopathy, rash, and other DMS manifestations (1). Our patient had vitreous cells in her right eye, supporting that phlebitis of the central retinal vein was the cause of her CRVO. She was admitted for evaluation of other causes of vasculitis, including lupus and sarcoidosis, which was unrevealing.

An alternative hypothesis is that DMS causes a systemic thrombotic microangiopathy resulting in CRVO. Sugimoto et al (21) reported a case of thrombotic microangiopathy associated with DMS that caused cutaneous vasculitis, renal hypertension, and occlusive retinopathy with cotton-wool spots and capillary obstruction. Similar findings also were reported in a child with juvenile DMS (22). However, in both cases, thrombocytopenia was a diagnostic sign of thrombotic microangiopathy. Our patient had a normal platelet count.

CRVO is associated with hypercoagulable states, such as pregnancy (23, 24), homocysteinemia, and antiphospholipid syndrome (25, 26). There is some evidence that patients with DMS have an increased rate of deep venous thrombosis, reported to be as high as 20%, although the mechanism is uncertain (27). Although CRVO can be

FIG. 1. Appearance of the right fundus is consistent with a central retinal vein occlusion, and the left fundus is normal.
a complication of hypercoagulable state with DMS, we believe that in our patient, thrombosis of the central retinal veins was due to phlebitis, supported by the finding of vitreous cells.

Our patient had the comorbid diagnosis of latent TB for which she had almost completed 8 months of INH. Given that TB has several known ocular complications including optic neuropathy (28), she had repeat QuantiFERON testing and cerebrospinal fluid acid-fast bacilli culture, both negative. We did not suspect her CRVO to be related to latent TB because she had no evidence of active disease and she was almost fully treated at the time of visual loss. We found no evidence of other causes for CRVO, including syphilis and HIV. Thus, we concluded that our patient’s most likely cause of her CRVO was a complication of DMS.

Because of the patient’s relatively good visual function, she most likely had a nonischemic CRVO. This conclusion is consistent with previously reported cases of CRVO in young patients (71%–73% nonischemic) (15). There are no standardized treatment protocols for nonischemic CRVO in young patients, although steroids have been suggested as a treatment option to suppress the proposed inflammatory mechanism (15). Because our patient was already taking prednisone, we deferred altering her corticosteroid therapy to her rheumatologist. The patient was observed for resolution of inflammation and management of the sequelae of CRVO. Macular edema secondary to CRVO was treated successfully with intravitreal bevacizumab injections. The elevation in IOP was most likely secondary to steroid use. Steroid-induced glaucoma is well characterized and typically presents within weeks of starting ophthalmic steroids but may present months after starting systemic steroids (29). Elevated IOP was first noted in our patient a month after she presented with the CRVO after 9 months of systemic steroid use.

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Tonsillar Herniation After Lumbar Puncture in Idiopathic Intracranial Hypertension

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Abstract: A 30-year-old woman with coexisting renal tubular acidosis and idiopathic intracranial hypertension (IIH), treated with acetazolamide, experienced coning (cerebellar tonsillar herniation) after a lumbar puncture (LP). Brain magnetic resonance imaging at initial diagnosis of IIH showed minor tonsillar descent and computed tomographic venography revealed hypoplasia of the left transverse sinus. The patient previously had three uneventful LPs, all of which showed high opening pressures and normal cerebrospinal fluid composition. In retrospect, it was noted that her serum bicarbonate had fallen to 9 mmol/L (normal: 22–28 mm/L) 1 week before the LP. We hypothesize that the combination of cerebral edema (due to worsening metabolic acidosis), poor venous drainage, and preexisting minor tonsillar descent contributed to her post-LP coning.

CASE REPORT

A 30-year-old woman was evaluated in our neurology clinic with a 3-month history of bifrontal and periorbital headache, associated with nausea and neck pain. Her headache was worse in the morning, on lying and on bending over. She also reported transient visual obscurations and nocturnal pulsatile tinnitus. Her medical history consisted of idiopathic distal renal tubular acidosis for which she was on sodium bicarbonate 3.36 g/d and potassium citrate 4.32 g/d.

The patient was morbidly obese with a BMI of 48.9 kg/m². Neurologic examination was unremarkable apart from bilateral papilledema. Visual acuity was normal but visual field testing showed enlarged blind spots and mild concentric field reduction bilaterally. On optical coherence tomography (CT), there was marked increase in the peripapillary retinal nerve fiber layer (RNFL) thickness (right eye: 280 μm; left eye: 356 μm). Computed tomography (CT) of the brain was normal, whereas magnetic resonance imaging (MRI) showed a partially empty sella and minor tonsillar descent (4 mm below the foramen magnum). LP performed under fluoroscopy revealed an opening pressure (OP) of 45 cmH₂O with normal CSF analysis (1 WBC, glucose 2.8 mmol/L, protein 182 mg/L). CT venography showed stenosis of the right transverse sinus and hypoplasia of the left transverse sinus (Fig 1).

The patient was prescribed acetazolamide 1 g/d without upward titration of her sodium bicarbonate and potassium citrate. Despite achieving an 11 kg weight loss, there was resolution of her papilledema, both clinically and on OCT (peripapillary RNFL thickness: right eye: 112 μm; left eye: 114 μm). Computed tomography (CT) of the brain was normal, whereas magnetic resonance imaging (MRI) showed a partially empty sella and minor tonsillar descent (4 mm below the foramen magnum). LP performed under fluoroscopy revealed an opening pressure (OP) of 45 cmH₂O with normal CSF analysis (1 WBC, glucose 2.8 mmol/L, protein 182 mg/L). CT venography showed stenosis of the right transverse sinus and hypoplasia of the left transverse sinus (Fig 1).
venous sinus stenting. Her OPs were persistently high but other CSF studies remained unremarkable.

Eight months later, the patient presented to the emergency department with a 1-week history of worsening headache. She had no visual symptoms but her papilledema had returned bilaterally. LP was repeated (single pass) using a 24 G Sprotte spinal needle, and OP was 43 cmH₂O. Twenty milliliters of CSF were removed resulting in immediate improvement of her headache. Seven hours later, the patient developed severe (10/10) global headache with excruciating neck pain. She was unable to lie flat, her back was arched and her neck was held in extreme extension. She subsequently developed severe hypotension, reduced level of consciousness, anisocoria, and bilateral extensor plantar responses. An urgent CT brain showed diffuse cerebral edema with transtentorial herniation and significant tonsillar descent (Fig 2). There was no change on CT venography.

The patient was intubated and transferred to the intensive care unit. An external ventricular drain and intracranial pressure (ICP) monitor were inserted. Her ICP continued to rise to more than 70 cmH₂O. Accordingly, she underwent urgent bifrontal craniectomy. CSF analysis on this occasion demonstrated 7 white cells (1 polymorphonuclear leukocyte, 6 mononuclear cells). CSF cytology and viral polymerase chain reaction (herpes simplex, varicella zoster, enterovirus) were negative. Her blood count, renal and liver function tests, sepsis screen (blood culture, urine culture, chest x-ray), and inflammatory markers were all normal. It was noted that her serum bicarbonate had fallen to 9 mmol/L (normal: 22–28 mmol/L) on routine testing 1 week previously. Her metabolic acidosis worsened at the time of her collapse, her arterial pH reaching a nadir of 7.19 (normal: 7.35–7.45) with an arterial pCO₂ of 19 mm Hg (normal: 35–45 mm Hg). She gradually recovered with no major neurological sequelae apart from some short-term memory loss and impulsivity. Future plans for her care include a shunting procedure and replacement of the cranial bone flap.

DISCUSSION

Minor tonsillar descent, defined as displacement of the cerebellar tonsils <5 mm into the upper cervical spinal canal, is well described in IIH. However, data on its prevalence are sparse and contradictory. In one case series of 43 patients with IIH, 28% of patients were reported to have mild tonsillar descent (2–4 mm) on MRI (4). This was similar to the 24% found in another study of 68 IIH patients (5), yet substantially higher than the 2.7% based on pretreatment MRI of 74 patients (6). Significant tonsillar herniation or coning remains very rare after LP (8). This complication occurs when there is significant displacement of the posterior fossa contents into the upper cervical canal leading to compression of the lower brainstem and upper cervical cord, CSF outflow obstruction, severe intracranial hypertension, and cerebral edema.

We could find only 1 case report of coning in a patient with IIH, which proved to be fatal (7). A 27-year-old woman previously diagnosed with IIH, presented with photophobia, neck stiffness, blurred vision, and scintillating scotoma while being treated for pneumonia. She underwent 2 lumbar punctures several hours apart. After the first LP (OP 45 cmH₂O), she demonstrated signs of coning including neck hyperextension, globally brisk reflexes, and bilateral extensor plantar responses. A second LP was performed (OP <25 cmH₂O) and, several minutes after this, she developed respiratory arrest, which led to her death. Autopsy was consistent with coning. Four years earlier, she had experienced respiratory arrest within minutes after an LP, and minor descent of the cerebellar tonsils was noted on her brain MRI.
The risk of coning in patients with IIH after LP was prospectively studied by Paruchuri et al (8). None of the 55 patients in their case series had significant tonsillar herniation (coning). They concluded that LP was safe in IIH but that caution should be applied in patients with severe neck pain exacerbated by movement, focal neurological signs, and minor tonsillar descent. The reason why coning is rare in IIH remains unknown. One hypothesis is that patients with IIH have a gradual reduction in brain compliance because of a combination of increased cerebral blood flow and mild diffuse interstitial edema (9–11). The subacute nature of IIH allows time for the brain to stiffen, thereby reducing its compliance (12). This may also explain why the ventricles do not enlarge despite chronically elevated CSF pressures within the ventricular system. They appear normal or slit-like on neuroimaging in contrast to other processes with similarly high intraventricular pressure. The difference may relate to the speed of onset of the conditions: a more rapid onset does not permit changes in periventricular brain tissue compliance, resulting in ventricular enlargement and periventricular edema (13,14).

Our patient re-presented with her usual headache pattern. Brain CT scan was not ordered before her LP because she had a normal scan 1 month before her admission and three previous LPs without incident. In retrospect, her metabolic acidosis, due to distal renal tubular dysfunction, had worsened with a sharp drop in her serum bicarbonate despite increased doses of sodium bicarbonate and potassium citrate. One neurological manifestation of acidosis is vasogenic cerebral edema, which results from increased cerebral blood flow due to cerebral vasodilation (15). Respiratory acidosis is a more common cause of cerebral edema than metabolic acidosis because of the ability of CO₂ to cross the blood–brain barrier easily, but both CO₂ and hydrogen ions can cause cerebral vasodilation. Inadequate treatment of our patient’s renal tubular acidosis combined with the use of acetazolamide most likely was responsible for the abrupt worsening of her metabolic acidosis, resulting in cerebral edema.

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STATEMENT OF AUTHORSHIP
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Progressive Multifocal Leukoencephalopathy: Recent Advances and a Neuro-Ophthalmological Review

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Background: Progressive multifocal leukoencephalopathy (PML) is a severe often fatal opportunistic infection of the central nervous system caused by reactivation of a ubiquitous polyoma virus, JC virus. Although typically characterized by multifocal asymmetric subcortical white matter lesions, it may be monofocal and affect the cortical gray matter. Among the broad spectrum of clinical manifestations that occurs with PML, visual complaints are common.

Evidence Acquisition: Combination of representative personally observed cases of PML and comprehensive review of case series of PML from 1958 through 2014.

Results: Neuro-ophthalmic signs and symptoms were reported in approximately 20%–50% of patients with PML and can be the presenting manifestation in half of these. A majority of these presentations occur from damage to cerebral visual pathways resulting in visual field defects, cortical blindness, and other disorders of visual association. Given the decreased frequency of infratentorial and cerebellar involvement, ocular motility disorders are less common.

Conclusions: Visual complaints occur in patients with PML and are often the presenting sign. Awareness of this condition is helpful in avoiding unnecessary delays in the diagnosis of PML and management of the underlying condition. Recent guidelines have established criteria for diagnosis of PML in the high-risk patient population and strategies to mitigate the risk in these populations.

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Progressive multifocal leukoencephalopathy (PML) was first described by Aström, Mancall, and Richardson in 1958 as a unique demyelinating disorder with characteristic histopathology in 3 patients with lymphoproliferative disorders (1). It is a severe often fatal demyelinating disease that results from lytic infection of oligodendrocytes by the JC virus, a ubiquitous human polyoma virus (2). PML usually occurs in the immunosuppressed patient and results in a devastating neurological illness which is fatal, unless the underlying immunosuppressive cause is identified and treated. Despite the propensity of PML to produce visual symptoms, very few reports have addressed the neuro-ophthalmological features of this disease. The objective of this review is to provide a current understanding of the disease process including the varied neuro-ophthalmic presentations using illustrative cases. For purposes of this report, we reviewed medical literature on Medline and Google Scholar using the terms PML, progressive multifocal leukoencephalopathy and vision, diplopia, pupils, eye movements, and blindness. Where appropriate, we also used data gathered by Bachmann and Mark (coauthors of this article) reviewing 240 cases of PML published up to 1992.

Epidemiology

PML is almost always observed in association with an immunocompromised state, either from an underlying disease or associated treatment; however, in rare instance, it may be seen in the absence of apparent immunological abnormality (3,4). The PML era can be broadly divided
into 4 epochs: pre-HIV, HIV (pre-HAART), HIV (post-HAART), and modern era. Before HIV epidemic in the early 1980s, PML was rare and seen almost exclusively in patients with lymphoproliferative and myeloproliferative disorders (5–10). After the HIV pandemic, the incidence of PML increased by almost 50-fold making HIV the leading cause of this disease (11–14).

During this era (HIV pre-HAART), 5% of patients with HIV developed PML with a median survival of 6 months with fewer than 10% survival rate 1 year after symptom onset. With the advent of highly active antiretroviral therapy (HIV post-HAART era), there was a significant decline in the incidence (15). Mortality rates from PML improved from 90% in the 1980–1990 decade to 50% in the first decade of the 21st century (16). A new era of PML dawned in 2005 when PML was reported in association with natalizumab for Crohn’s disease and multiple sclerosis (MS) (17–19). This resulted in a temporary withdrawal of natalizumab, an anti-alpha-4 integrin, from the market in 2005. Of 99,517 patients treated with natalizumab until 2012, there were 212 confirmed cases of natalizumab-associated PML (20). Other than natalizumab and efalizumab, PML has also been reported with various monoclonal antibodies and immune-modifying therapies. Among other immunomodulatory agents that have implicated in predisposing to PML are the anti-TNF-alpha agents, infliximab, adalimumab, and etanercept, ruxolitinib (inhibitor of JAK 1 and 2), and oral agents used in treatment of MS, dimethyl fumarate (Tecfidera) (21,22). Currently, several drugs carry an FDA-mandated black box warning for PML, including natalizumab, rituximab, brentuximab–vedotin, and mycophenolate mofetil.

Pathogenesis
Subclinical infection with JC virus generally occurs within the first decade of life and by adulthood; 50%–80% of the population is seropositive for the virus (23,24). The virus remains latent in the kidney, bone marrow, and lymphoid organs (8). PML is caused by reactivation of the JC virus in the setting of immunosuppression with spread to the CNS leading to oligodendrocyte infection and demyelination. JC virus infection of the brain typically causes a subacute progressive disorder with multifocal asymmetric subcortical white matter involvement from which the disease entity derives its name. Astrocytes and neurons may also be infected but the virus does not complete its entire replicative cycle in the former. Instances of monofocal disease and gray matter involvement of cerebellar granular cells (25,26) and cerebral cortical neurons have been described (27). Isolated lesions of the cerebellum and brainstem are rare [Joseph Berger, MD and 2013 personal observation and Mossakowski and Zelman (28)] and may be higher in the HIV/AIDS population with PML (12) compared with other predisposing causes such as natalizumab-associated PML (29).

Clinical Presentation
Despite a propensity to affect the cerebral hemispheres, any part of the brain may be affected, which produces a variety of neurological manifestations. Behavioral and cognitive abnormalities are seen in one-third to half of all individuals (12,29). Common findings include motor weakness, gait abnormalities, visual field defects, language problems, and incoordination (12,30). Less common findings include headache, sensory loss, seizures and diplopia (12,30). Spinal cord involvement has only been reported in pathologic specimens; myelopathy has not been described clinically (31). There are no descriptions of optic nerve disease or peripheral nervous system involvement by PML. Despite significant overlap in clinical presentation, cognitive problems more often herald natalizumab-related PML, whereas motor weakness is associated with HIV-related PML (29).

Neuro-ophthalmology of PML
Very few studies in literature have systematically described the neuro-ophthalmic features of PML (32,33). Brooks and Walker (30) reviewed 230 published and unpublished cases of PML and reported visual field deficits (34.7%), visual blurring (7.2%), diplopia (1.4%), optic atrophy (1.4%), and cortical blindness (2.9%). Only 45% of these were virologically or pathologically confirmed cases. Berger and Pall (12) reported visual field defects (19%) and diplopia (9%) in their series of 154 HIV-associated patients with PML at presentation. In their review of 240 published cases of PML, Bachman and Mark found 125 patients (52%) with neuro-ophthalmological findings (2–7,11,34–138). Of the 74 patients with AIDS, 40 (54%) had neuro-ophthalmological findings (See Supplemental Digital Content, Table E1, http://links.lww.com/WNO/A163). Visual disorders can be the presenting features in approximately 20% of patients with both HIV-associated and non–HIV-associated cases of PML (10–12,41,120,139–142). In the following sections, we will describe the pertinent neuro-ophthalmological features using illustrative cases.

Case 1
A 63-year-old woman with a history of Sjogren’s syndrome and ovarian cancer developed difficulty reading a clock face and began bumping into objects in her left visual field. Her symptoms were initially attributed to “chemobrain”; but 3–4 months later, she developed stuttering, difficulty folding clothes, tying her shoes, and dressing herself, followed a month later by left arm and leg weakness. Neurological examination showed dyscalculia, difficulty following three-step commands, dressing apraxia, dense left homonymous hemianopia, and mild left hemiparesis. Brain magnetic resonance imaging (MRI) obtained 2 months later showed a large T2/fluid-attenuated inversion recovery image (FLAIR) hyperintense signal abnormality affecting the right parietal and occipital lobes with extension across splenium.

of the corpus callosum (Fig. 1). There also was involvement of the right thalamus, posterior limb of internal capsule, and right cerebral peduncle. The lesion was hypointense on T1 imaging, did not enhance with contrast, was subcortical in location, and did not demonstrate mass effect. CSF examination showed JC virus DNA by polymerase chain reaction (PCR technique). She had an absolute CD4 count of 390 cells per microliter and CD4/8 ratio of 0.5.

Homonymous Hemianopia
Homonymous hemianopia (including quadrantanopia) is the most common ophthalmic manifestation of PML from involvement of optic radiations in both AIDS and non-AIDS series, seen in 25% of the 240 cases of PML reviewed by Bachman and Mark through 1992 (See Supplemental Digital Content, Table E1, http://links.lww.com/WNO/A163). Other studies have reported higher figures (35%–45%) for homonymous hemianopia in reported cases of PML (30,32). Unilateral and bilateral homonymous hemianopia and quadrantanopia may be the presenting symptom of PML in AIDS (33,142,143). Reversal of both vision and other neurological deficits 8 months after resumption of highly active antiretroviral therapy (HAART) was reported in patients with HIV-associated PML (144,145).

Homonymous hemianopia also has been reported in cases of PML from natalizumab. In a series of 28 patients with natalizumab-associated PML, 5 had homonymous hemianopia and 3 reported diminished vision as a presenting manifestation (29). Homonymous hemianopia in patients with MS on natalizumab should raise suspicion for PML. This has prompted recommendations for visual acuity and visual field testing every 3 months in patients with MS treated with natalizumab for 1 year or longer (146).

Case 2
A 35-year-old man with a history of HIV and non-Hodgkin’s lymphoma, in remission for 7 years after treatment, developed dizziness, confusion, and blurred vision. He discontinued HAART 3 years earlier and was lost to follow-up. For the last 3 months, he had difficulty driving and had sideswiped cars on his right side. Neurological examination performed 1 month later was remarkable for cortical blindness, visual agnosia, pure word deafness, and right hemiparesis. MRI brain showed T2/FLAIR hyperintense signal in the left parietal and occipital lobes and splenium of corpus callosum (Fig. 2). There was extension into the left posterior frontal lobe, external capsule, and posterior limb of the internal capsule, thalamus, mid-brain, pons, and contralateral occipital lobe. Most recent CD4 count was 26 cells per microliter, CD4:CD8 ratio was 0.18, and HIV viral load was 74,800 copies per mL. CSF examination confirmed JC virus DNA by PCR technique. Biopsy of the occipital lesion showed features that were consistent with PML (Fig. 3).

Abnormalities of Visual Association
A large spectrum of disorders of visual association has been observed with PML including visual neglect (12), visual hallucinations (147), prosopagnosia, and impaired spatial perception (12,139). Balint syndrome (148–151) has been reported in patients with PML. These patients frequently complain of visual distortion, difficulty reading, “fragmented” environment, difficulty driving, and other visuospatial abnormalities. In those instances in which Balint syndrome has been attributed to HIV encephalopathy, it is far more likely to have been caused by unrecognized coexisting PML (152,153). Bachman and Mark have seen 2 patients with optic aphasia in
association with alexia and homonymous hemianopia. Both had involvement of the dominant parietal lobe and corpus callosum producing the “disconnection syndrome.” These patients had presented with difficulty reading and naming letters on the Snellen chart despite 20/20 visual acuity.

Cortical blindness in PML results from bilateral involvement of the retrogeniculate visual pathways, typically the optic radiations or the primary visual cortex and may be seen in 6%–8% patients (30,41). These cases may start with visual blurring and progress to visual field loss and cortical blindness, as unchecked PML progresses to bilateral occipital involvement often accompanied by neurological deficits such as prosopagnosia and alexia with agraphia (139). Unless there is a high degree of suspicion, presentation of PML as visual loss may be mistakenly attributed to ophthalmic causes such as cataract or postoperative inflammation after eye surgery leading to unnecessary procedures and diagnostic delay (154,155).

**Case 3**
A 34-year-old homosexual man with a 12-year history of AIDS and no previous opportunistic infection reported a 2-week history of right face and arm paresthesia, numbness, and weakness. One week before presentation, he developed blurred vision and binocular vertical diplopia. He had discontinued HAART 1 year ago due to intolerance to medications. On examination, he had right hemiparesis, right central facial palsy, and left hypertropia (consistent with skew deviation). Visual acuity, visual fields, pupillary reflexes, and retinal examination were normal. Brain MRI showed a T2 hyperintense lesion in the left pons extending to the left cerebral peduncle (Fig. 4). There also was involvement of the centrum semiovale bilaterally. Lumbar puncture demonstrated 5 white blood cells per mL, 1093 red blood cells per mL (traumatic tap), protein of 86 mg/dL (normal: 15–60 mg/dL), glucose of 58 mg/dL (normal: 15–45 mg/dL), and 120
copies per mL of JC virus DNA by PCR. In his blood, he had 120,000 copies per mL of HIV-1 RNA.

**Infratentorial PML**

Infratentorial demyelinating lesions may occur in isolation or with supratentorial lesions (12,109,156–158). The cerebellum is more commonly involved than the brainstem probably as a consequence of greater volume and due to a unique cerebellar syndrome from the causative virus referred to as JC virus granule call neuronopathy (159). Patients with brainstem findings may have concurrent involvement of the cerebellum seen on imaging or on pathological investigations (157). Infratentorial (cerebellar and brainstem) abnormalities were noted on neuroimaging studies in 48% (20% isolated infratentorial lesions) of 154 PML cases in a large series (12). Infratentorial involvement on imaging studies does not necessarily translate to clinical abnormalities in as many as 50% of cases. This poor correlation could be artifactual (retrospective studies, brainstem signs either not elicited or recorded) or related to the natural history of the disease with chances of brainstem involvement being less when duration of PML is less than 2 and half months (109).

Brainstem involvement may cause nuclear, internuclear, and supranuclear palsies producing diplopia, facial weakness, and numbness, hypoacusis, dysarthria, dysphagia, and nystagmus. PML may cause isolated or multiple ocular motor cranial neuropathies, multiple cranial neuropathy (sixth and seventh), internuclear ophthalmoplegia (160), or abnormalities of ocular smooth pursuit, saccades, and nystagmus (12,161). PML with cerebellar JC viral granular neuronopathy may present with a combination of cerebellar and brainstem signs such as ataxia, nystagmus, diplopia, dysarthria, dysphagia, and vertigo (51,65,77,88,136,157,162,163). PML causing progressive brainstem disorder was reported in a patient with systemic lupus erythematosus being treated with etanercept and prednisone after she presented with diplopia, right face hypoesthesia, vertigo, dysarthria, right hemiparesis, hemiataxia, and gait problems. Brain MRI demonstrated lesions of bilateral pons and medulla, right middle cerebellar peduncle extending into the right cerebellar hemisphere, and left paramedian cerebellum (164).

**Optic Nerve**

Primary involvement of the optic nerve has not been reported in PML, which is surprising because the JC virus targets the oligodendroglia, which produces optic nerve myelin. Optic atrophy is usually secondary to underlying cause such as MS (5). The latter is particularly true in the patients with MS who have developed natalizumab-associated PML. Curiously, Brooks and Walker (30) in their review of 230 cases of PML, which predated the use of natalizumab for MS found optic atrophy in 1.4% of cases at the time of diagnosis.

**DIAGNOSTIC CONSIDERATIONS**

Demonstration of the JC virus in brain tissue or CSF is insufficient for diagnosis of PML because the virus may be found in these locations of normal individuals. Diagnostic criteria for PML have been published as a consensus statement from the American Academy of Neurology's Neuroinfectious Disease Section (See Supplemental Digital Content, Table E2, http://links.lww.com/WNO/A164) (165). The 2

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**FIG. 4.** Case 3: Magnetic resonance imaging of progressive multifocal leukoencephalopathy. A. Top panel, Axial fluid-attenuated inversion recovery images reveal hyperintensive lesion in left pons extending into left cerebral peduncle (arrows). Bottom panel, Postcontrast T1 axial scans show the lesion to be hypointensive with enhancement. B. Top panel, Axial diffusion-weighted imaging shows the lesion to be hyperintense. Bottom panel, apparent diffusion coefficient (ADC) images fail to show evidence of restricted diffusion.
diagnostic approaches used include demonstration of typical histopathological findings and JC virus in tissue specimen or a demonstration of JC virus in the CSF of patients who fulfill clinical and radiographic criteria. The characteristic histopathologic features of PML include multifocal demyelination, enlarged bizarre astrocytes with lobulated hyperchromatic nuclei, and enlarged oligodendroglial nuclei. The presence of JC virus in the specimen can be confirmed by electron microscopy, immunohistochemistry, or PCR techniques.

The imaging characteristics of PML are not diagnostic. Hypodense white matter lesions without mass effect or contrast enhancement are seen on computed tomography. Brain MRIs show hyperintense white matter lesions on T2 and FLAIR images, which are hypointense on T1 images. Gadolinium enhancement is seen in 15% of HIV-associated PML and 40% of natalizumab-associated PML (166).

TREATMENT

Although there is no definitive pharmacological treatment for PML, management is aimed at reversal of the underlying immunosuppressive state, which includes treatment with HAART in patients with HIV/AIDS and removing offending immunosuppressive agents, such as natalizumab. Risk mitigation strategies used to prevent the development of PML include monitoring patients on natalizumab for JC virus antibody, limiting the cumulative total dose in those that are JC virus antibody positive and serial brain MRI scans to detect PML early (167). In JC virus antibody–positive individuals, the risk of PML after 24 months of treatment with natalizumab is as follows: in those without previous immunosuppressant use, the risk is estimated at 3 per 1000 and in those with previous immunosuppressant use, it is 13 per 1000 (https://medinfo.biogenidec.com). Discontinuing natalizumab in these circumstances requires an informed discussion with the patient. Although increasing the time interval between doses of natalizumab has been suggested to decrease the occurrence of PML, there are no well-controlled trials to demonstrate the efficacy of this strategy. There is no consensus about the drug of choice after natalizumab discontinuation. A patient with PML after dimethyl fumarate (Tecfidera) treatment has been reported in the absence of other prior or concomitant immunomodulatory therapy (Tecfidera product label, December 2014). A combination of lymphopenia and reduced leukocyte binding to VCAM by 33% induced by dimethyl fumarate (168) may underlie an increased risk for PML. These observations coupled with reports of PML with fumaric acid esters in the treatment of psoriasis raise concerns about its use in this population (21,22).

CONCLUSIONS

The neuro-ophthalmic manifestations of PML are protean and depend on the parts of the nervous system affected. Impaired vision from lesions of retrogenticulate visual pathway and association cortices appears to be one of the most common manifestations of PML. Ocular motility disorders result from involvement of the brainstem and cerebellum. Without awareness of these presentations, the diagnosis of PML may be missed in those patients who initially are seen by an opthalmologist or neurologist with visual complaints. Approximately one-third of patients with PML present with visual disturbances. Homonymous hemianopia is the most common neuro-ophthalmological manifestation; however, a wide variety of abnormalities of afferent and efferent visual systems are observed. Visual complaints may not only herald PML but are frequently the most debilitating symptom.

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State-of-the-Art Review


Paraneoplastic Syndromes in Neuro-Ophthalmology

Lynn K. Gordon, MD, PhD

Background: Paraneoplastic syndromes that affect the visual pathways and present with neuro-ophthalmologic signs or symptoms may involve the afferent or efferent systems. Afferent syndromes may involve the optic nerve or retina and, in some cases, these may be associated with systemic neurologic disease. Efferent symptoms typically affect eye movements and may involve the neuromuscular junction or involuntary eye movements.

Evidence Acquisition: Literature review and personal clinical and research experience.

Results: Diagnosis of paraneoplastic syndromes relies on clinical and laboratory evaluations. In the appropriate clinical setting, the presence of specific antibodies may help confirm the diagnosis.

Conclusions: In some cases, the visual pathway disturbance precedes a diagnosis of malignancy. Astute observation and selective evaluation and management are critical to establish the correct diagnosis and institute therapeutic approaches that can be sight or life saving.

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Paraneoplastic syndromes may affect the afferent and efferent visual pathways and involve the retina, optic nerve, or eye movement systems (1–6). In some cases, the neuro-ophthalmic consequences are the first indication of a malignancy, and in others, the visual pathways are affected in patients with known malignancies. The challenges are to recognize when a symptom or sign may be associated with an underlying malignant disease, to understand the diagnostic challenges in identifying an underlying paraneoplastic cause for the observed visual pathway deficits, and to determine the optimal strategy for therapeutic intervention. It is important to understand the spectrum of signs and symptoms that can result from a tumor-stimulated immune process to suspect, diagnose, and treat these diseases.

Clinical Disease Spectrum

When should the clinician consider a diagnosis of paraneoplastic syndrome? (1.6–11). In terms of afferent symptoms, an unexplained, painless, progressive vision loss is typical. With retinal involvement, there may be photopsias, night blindness, or ring scotomas. In the optic neuropathies, there is most commonly bilateral disc swelling often accompanied by vitritis. Efferent symptoms include myasthenia-like presentation or the presence of opsoclonus/myoclonus syndrome (OMS). Associated systemic neurologic symptoms, such as encephalitis, cerebellar degeneration, myelitis, or sensory neuropathies, increase suspicion for a paraneoplastic syndrome. Pertinent negatives include lack of alternative explanation for the symptoms such as a known genetic condition, history of ocular surgery, infection, trauma, mass lesion, or toxic exposures. This review does not focus on syndromes associated with anti-Hu, anti-Ma, and anti-Yo as these typically manifest with a variety of brainstem and cerebellar findings. A history of cancer may heighten the suspicion for a paraneoplastic syndrome, but the real challenge is to diagnose a potentially treatable cancer in patients who do not already carry that diagnosis.

Afferent Symptoms

Autoimmune Paraneoplastic Retinopathy

Three types of autoimmune paraneoplastic retinopathy syndromes have been described: cancer-associated retinopathy (CAR), melanoma-associated retinopathy (MAR), and bilateral diffuse uveal melanocytic proliferation (BDUMP) (12–19).

CAR was the first of these syndromes to be recognized, seems to be the most common of the paraneoplastic retinopathies, and remains a significant diagnostic and therapeutic challenge (12). Visual dysfunction in CAR typically involves a bilateral, progressive, and painless loss of vision with photopsias (14,20) Patients complain of a rapid onset of night blindness and flickering lights associated with progressive vision loss over weeks to months. The signs and symptoms depend on whether rod or cone function is
primarily disrupted. In rod disease, there is often constriction of the visual field with impaired dark adaptation (Fig. 1). In contrast, when there is primarily cone dysfunction, central scotomas, dyschromatopsia, glare, and loss of visual acuity are more prominent. There may be an associated uveitis involving the anterior segment or vitreous, and this may also include retinal vasculitis and cystoid macular edema (9). Retinal findings may be unexceptional. Alternatively, arteriolar narrowing, thinning or mottling of the retinal pigment epithelium (RPE), or pallor of the optic disc may be observed in these patients. Electroretinography (ERG) confirms photoreceptor dysfunction but is not pathognomonic for CAR. ERG shows reductions in the amplitude of the scotopic and photopic a- and b-waves, and in some cases, a negative waveform is observed. Fluorescein angiography may reveal cystoid macular edema or retinal vasculitis. Optical coherence tomography (OCT) may demonstrate macular atrophy with photoreceptor...

FIG. 1. Paraneoplastic retinopathy. An 81-year-old woman complained of decreased vision, impaired light adaptation, and progressive visual field loss. She had a history of breast cancer treated 4 years earlier with lumpectomy, chemotherapy, and radiation therapy and was cancer free at the time of evaluation. On examination, visual acuity was 20/20 in the right eye and 20/50 in the left eye with constricted visual fields. Ophthalmoscopy was unremarkable (A and B), but optical coherence tomography shows cystoid macular edema in the right eye (C) and vitreomacular traction in the left eye with possible early lamellar hole formation (D). ERG showed a significantly truncated b-wave consistent with downstream dysfunction (E). Anti-retinal antibody testing was positive on Western blot for aldolase antibodies and, on immunohistochemistry, for antibodies against bipolar cells and the inner plexiform layer. This case highlights the importance of ERG evaluation in patients despite the presence of other retinal abnormalities such as cystoid macular edema or vitreomacular traction in the diagnosis of retinal dysfunction (Courtesy of Michael Gorin, MD, PhD). ERG, electroretinography.
thinning and loss of inner/outer segment junction. CAR may occur in patients with known malignancies, but it also may occur before the diagnosis of cancer. Thus, prompt recognition may lead to early diagnosis and cure for patients with specific types of malignancies. Although the most common tumor associated with CAR is small cell lung carcinoma, other tumors originating in many organs including the prostate, bladder, colon, thymus, ovary, endometrium, breast, and cervix also have been implicated in CAR (Table 1).

Visual symptoms in MAR have rapid onset and include loss of visual acuity, presence of photopsias, and central or paracentral scotomas (21,22). Vision loss is usually mild with the majority of patients having a best-corrected visual acuity in the 20/60 range. Ophthalmoscopy initially may be normal but may show optic atrophy, retinal vascular attenuation, or loss of RPE. ERG abnormalities typically include an electronegative pattern with a normal dark-adapted a-wave and attenuated or absent b-wave (Fig. 2). In a large review of more than 60 patients with MAR, vitreous cells were present in 30% of affected patients (22). However, the fundus evaluation was initially normal in more than 40%. Similar to CAR, disc pallor and retinal vascular attenuation may be observed. Patients with MAR usually have a diagnosis of malignant melanoma that typically predates the retinal disease by several years. Cases of MAR have been primarily associated with cutaneous melanoma but have also been observed in patients with ocular or mucosal sites for the primary tumor, thus necessitating a thorough systemic evaluation for tumors in those patients without a known melanoma.

BDUMP is rare but distinctive in its proliferation of melanocytes in the uveal tract along with bilateral loss of vision. These patients experience sudden and bilateral visual loss and may have exudative retinal detachment and progressive cataracts. Patients with BDUMP typically have a short life span, less than 15 months after diagnosis on average. Visual disturbance may precede diagnosis of malignancy, and although multiple types of cancers have been identified in association with BDUMP, the most common are lung, colon, pancreas, or gynecologic. OCT is helpful in identifying subretinal fluid. Areas of RPE atrophy and adjacent regions of RPE hypertrophy are typical and seen well on fluorescein angiography.

**Paraneoplastic Optic Neuropathy**

Paraneoplastic optic neuropathy (PON) is an unusual but serious cause of bilateral painless loss of vision. Vision loss is typically subacute, occurring over days to weeks. In 2003,
Melanoma-associated retinopathy. A 76-year-old man noted vibrating and sparkling visual symptoms associated with reduced night vision. His history was significant for a malignant melanoma removed approximately 5 years earlier. ERG tracings show the photopic (A) and scotopic (B) responses and demonstrate the characteristic decrease in the b-wave under scotopic conditions (label 2 in [B]) (Courtesy of John Keitner, MD). ERG, electroretinography.

FIG. 2. Melanoma-associated retinopathy. A 76-year-old man noted vibrating and sparkling visual symptoms associated with reduced night vision. His history was significant for a malignant melanoma removed approximately 5 years earlier. ERG tracings show the photopic (A) and scotopic (B) responses and demonstrate the characteristic decrease in the b-wave under scotopic conditions (label 2 in [B]) (Courtesy of John Keitner, MD). ERG, electroretinography.

A cohort of 16 patients was identified as being positive for the antibody against collapsin response-mediating protein 5 (CRMP-5) (11). Similar to patients with CAR and MAR, photopsias may be present. Ophthalmoscopic findings include optic disc edema and vitreous cells, but patients may present with optic atrophy as well. Retinitis also may be present, and in these patients, the ERG may show scotopic or photopic abnormalities. Vitreous cells appear small, without clumping, and without evidence for an intermediate uveitis, and are typically pleomorphic lymphocytes. One of the original 16 patients also had anterior chamber cells, an unusual finding in this disease. The histopathology of the optic nerve in affected cases demonstrates inflammation of the optic nerve with lymphocytic infiltrates. In one case the infiltrating cells were primarily CD8+ T cells and in another case they were identified as both T cells (CD3+) and B cells (CD20+) (11,23). In addition, disorders of eye movement including vertical gaze disturbance, internuclear ophthalmoplegia, and opsoclonus have been observed in affected patients.

Systemic neurologic symptoms are present in essentially all patients during their illness and may include seizures, cognitive abnormalities, dementia, cerebellar findings, and a wide variety of motor and sensory abnormalities (24). Evaluation of the spinal fluid in patients with PON may reveal lymphocytosis or elevated protein (11). The most common cancer in these patients is small cell lung carcinoma but also includes neuroendocrine tumors, nasopharyngeal carcinoma, and colon cancer, among others (25–28). One reported patient with unilateral sudden loss of vision due to an optic neuropathy had a choroid meningioma. There was immune seroreactivity against optic nerve sections from multiple species and reversal of the optic neuropathy after tumor resection, suggesting a cause and effect relationship with this tumor (29).

POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome) should be included when considering the paraneoplastic afferent syndromes that present with neuro-ophthalmologic signs or symptoms. Major criteria include a monoclonal plasma cell dyscrasia and polyneuropathy, initially sensory but ultimately both sensory and motor. Bilateral optic disc edema is observed in about half of the patients with POEMS, and this may be asymptomatic (29% of patients) or alternatively may be associated with symptoms of blurred vision, pain, or double vision (9,30,31). Evaluation of the cerebrospinal fluid (CSF) often shows an increased opening pressure and elevated protein. The mechanism of ophthalmologic signs and symptoms in POEMS is likely distinct from the other paraneoplastic diseases and may involve high levels of inflammatory cytokines or vascular endothelial growth factor. Specific immune mechanisms, including cellular or humoral immunity, leading to this syndrome have not been implicated.

Efferent Symptoms

Opsoclonus/Myoclonus Syndrome

Although abnormalities of eye movement associated with paraneoplastic disease include disorders of saccades and smooth pursuit, opsoclonus/myoclonus, and nystagmus, the best characterized is the opsoclonus/myoclonus syndrome (OMS).

Myoclonus is defined by short sudden involuntary jerking movements, which may involve lower or upper extremities, trunk, or face and may be induced or worsened by a change in posture or stress (32–37). Opsoclonus is the ocular equivalent of myoclonus and is characterized by rapid, involuntary, horizontal, and vertical conjugate eye movements without intersaccadic delay (A video of a patient with paraneoplastic opsoclonus can be viewed on the NOVEL Web site at http://content.lib.utah.edu/cdm/singleitem/collection/ehsl-shw/id/92/rec/12). In children, up to 43% of cases of OMS are associated with a paraneoplastic syndrome linked to neuroblastoma (38). However of all patients with neuroblastoma, only 2%–4% will develop OMS. Other etiologies during childhood include ovarian teratoma, hepatoblastoma, or infections including mycoplasma pneumonia and hepatitis C.

In 2012, a series of 21 adults with OMS was published in conjunction with a review of all reported cases at that time of adult OMS (n = 116) (35). The age range for newly reported patients was 27–78 years, and symptoms consisted...
of dizziness/balance difficulties in 67%, nausea/vomiting in 48%, and abnormalities of vision from opsinclonus in 28%. Neuroimaging was normal in all except one patient with metastatic disease. Evaluation of CSF revealed abnormalities in more than 50% of patients including elevated protein and/or increased white cells (lymphocytes); in about one-third of cases, there may be an increased IgG index or oligoclonal bands (32,35). Cancer was identified in about half of the reported cases, and although small cell lung cancer was the most common, other malignancies included non–small cell lung cancer, breast adenocarcinoma, and ovarian carcinoma. Several adult patients with OMS were found to have thymic carcinomas, one in whom the OMS significantly improved after surgical removal of the tumor (39). Ocular flutter also has been associated with lung and breast cancer and, therefore, a thorough neoplastic evaluation is indicated in these patients (40). The majority of nonmalignant causes of OMS include parainfectious etiologies such as infection with HIV.

Lambert–Eaton Myasthenic Syndrome
In the Lambert–Eaton myasthenic syndrome (LEMS), there is a decrease in acetylcholine release leading to decreased activity of the neuromuscular junction. Although LEMS is typically characterized by decreased deep tendon reflexes, autonomic dysfunction, and proximal muscle weakness, symptoms of diplopia and ptosis are common (5,7). Autonomic symptoms develop in about 90% of affected patients within the first 3 months of disease onset and are very helpful in establishing the diagnosis as LEMS. To distinguish LEMS from myasthenia gravis (MG), clinical findings, such as slight increases in strength on prolonged effort, and electromyography, showing facilitation in repetitive stimulation testing, are helpful when present. Ocular symptoms generally occur after onset of other disease symptoms such as generalized weakness and ultimately occur in about half of the patients with LEMS. Ocular findings reported in patients with LEMS, that are not generally seen in MG include involuntary lid closure, decreased ptosis with prolonged upgaze, dilated pupils, and poorly reactive pupils (5). Ductions are typically full in LEMS but may be limited in MG patients. More than 50% of patients with LEMS not only have cancer, commonly lung cancer, but also lymphoproliferative diseases as well as cancers of the prostate or thymus may be present.

PATHOPHYSIOLOGY
The paraneoplastic syndromes often involve antibodies against normal proteins that are also typically expressed in the tumor. Some syndromes are also associated with tissue infiltration of inflammatory cells. To date, a virtual alphabet soup of proteins have been identified as potential immune targets, and in some cases, these proteins have been validated as playing a significant role in the pathophysiology of the disease (Table 1). For other candidates, the physiological role played by the immune response against a particular autoantigen is not entirely clear.

Recoverin, a 23 kDa protein, was the first antigenic target identified in patients with CAR. The protein is widely expressed in the majority of lung cancer samples, irrespective of retinopathy. Serum autoantibodies against recoverin may be present in a small subset of patients with lung cancer, but only a small fraction of those develop CAR. Alpha-enolase, another common protein that is found both in lung cancer and the retina, elicits an antibody in a larger percentage of patients with lung cancer (estimated at 13%–65%); however, only a small subset of these patients will develop CAR (1,41,42). Alpha-enolase antibodies also are found in many other diseases, including autoimmune hepatitis, rheumatoid arthritis, and mixed cryoglobulinemia. In addition, these antibodies may be found in normal individuals; thus, their presence alone does not indicate disease or causation of symptoms.

How are these antibodies associated with disease pathophysiology? It is believed that high-titer of antibodies may traverse the blood–retinal barrier, leading to exposure to retinal cells. There is also some evidence for different antigenic epitopes within a protein with differential consequences with regards to pathology. In addition, the immunologic phenomenon of epitope spreading may be associated with differences in pathogenic sequelae. In the retina, there is some evidence that the antibody may be engulfed through an endocytic mechanism into retinal cells (43). Once internalized, the antibody engages its corresponding antigen, and this binding leads to downstream signaling resulting in apoptotic cell death. This observation was initially made in vitro using retinal cells in culture but has also been replicated in vivo using either intravitreal or intravenous injections of antibodies against recoverin. Apoptosis was activated through caspase 3 and caspase 9 (44). It is believed that an increase in free Ca$^{2+}$ precedes apoptosis, a mechanism that was also observed in studies using antibodies against enolase. In studies using anti-enolase antibodies, there is a decrease in glycolytic adenosine triphosphate with resultant increase in the intracellular Ca$^{2+}$. This mechanism is a plausible common pathway leading to cell death. However, additional studies will be required to definitively understand the disease pathophysiology. Many other potential antigens also have been identified, but it is yet unknown whether the antibodies against these antigens play an important role in disease pathogenesis.

In LEMS, there is a well-characterized antibody against P/Q voltage-gated calcium channels (VGCC), present on the presynaptic nerve terminal at the neuromuscular junction. This antibody reproduced the disease in animal models, present on the presynaptic nerve terminal at the neuromuscular junction. This antibody reproduced the disease in animal models, and the disease can be transmitted passively from mother to child. It is believed that the antibody causes a loss in the VGCC, leading to a decrease in Ca$^{2+}$ internalization and decrease in release of acetylcholine containing vesicles, with less available acetylcholine at the neuromuscular junction.
PATIENT EVALUATION

For the well-characterized antigens in disease pathophysiology, such as CRMP-5 and recoverin, the presence of antibodies is helpful in making the diagnosis. The challenges are primarily 1) interpreting and identifying possible disease-associated antibodies against other possible antigens and 2) understanding the sensitivity and specificity for the known antigens in making the diagnosis of a paraneoplastic disorder. Laboratory evaluations for the presence of antibodies are performed using multiple techniques including immunofluorescence against tissues, immunofluorescence against cultured or purified cells, Western blot against proteins extracted from tissues or cells, and enzyme-linked immunosorbant assay (ELISA) testing against purified proteins. The potential pitfalls of testing include the tissue or cells of origin, the way that the proteins are extracted from the tissue or cells, the dilution and exposure time to the patient serum, techniques to enhance specificity, and the size of the antigen of interest. In all of these tests, it is important to understand the limitations of the testing strategy and the false-positive and false-negative potential for a particular technique.

Antibodies against self-proteins are fairly common. Using Western blot analysis, the majority of normal individuals have immunologic reactivity against at least 1 protein in whole retinal extracts (45). In a review of the literature about anti-retinal antibodies, it was pointed out that standardization among laboratories was lacking and results were not always concordant between different testing sites (46). This was confirmed in a report of 14 patients who were diagnosed with autoimmune retinopathy (47). Their serum was sent to 2 different laboratories for evaluation of the presence of anti-retinal antibodies by Western blot. One laboratory used human retina extract with a positive control, and the other used pig retinal extract with a panel of normal controls (without anti-retinal activity). Anti-retinal antibodies were detected in 9 patients by both laboratories. In the remaining 5 patients, 4 were positive for anti-retinal antibodies as detected by one laboratory and one was positive as detected by the other laboratory. Furthermore, for the 9 who were positive, there was only a single patient whose sera gave the same results (within 1 kDa of size of the band) from both laboratories.

What Antibodies Are Known to be Disease Associated?

Disease-associated validated antigenic targets of antibodies have been described in several of the paraneoplastic neuro-ophthalmic syndromes (Table 1). However, there are other antigens that have also been identified as potential immunologic targets, but the pathologic significance of these antibodies is uncertain. What testing is recommended when you encounter a patient with a suspected paraneoplastic syndrome with neuro-ophthalmologic symptoms?

If you suspect CAR, then antibodies against retinal proteins initially should be tested with Western blot and/or immunofluorescence. As noted above, however, it might be important to send materials to different laboratories for investigation. In one large series of CAR patients, only 61% had antibodies against defined retinal proteins, of which the antigenic targets were alpha-enolase in about half of the patients, followed in descending order by transducin, carbonic anhydrase II, and recoverin (1). Antibodies against recoverin, the best characterized antibody, were found in only 10% of the patients. If the clinical suspicion for CAR remains high, but the antibody testing is negative, then one might try empirical therapy for treatment of CAR, in particular in the setting of known malignancy, to determine whether there is clinical improvement.

If the testing is negative, consider the possibilities that the patient is negative for anti-retinal antibodies or that the technique used was not sufficiently sensitive to uncover the reactivity. If antibody testing is positive, you need to determine whether the results fit the observed clinical picture before making the diagnosis. For example, anti-recoverin antibodies, the best-studied antibody associated with CAR, have been observed in 1% of patients with retinitis pigmentosa (12). Multiple anti-retinal antibodies may also be found in the same patient (48).

Patients with MAR most commonly produce antibodies that react with retinal bipolar cells, as visualized by immunofluorescence. However, specific antigenic targets are not well-defined although several candidate antigens have been identified (22) MAR patients serum may also exhibit immunoreactivity against other retinal layers. Therefore, MAR is primarily a clinical diagnosis, based on the presenting signs and symptoms, a history of melanoma, and ERG findings that are consistent with the disease. If there is no history of melanoma, but your clinical suspicion is high for MAR, then the patient should be referred for dermatologic evaluation and possibly additional testing, such as body position emission tomography (PET) imaging.

In cases of PON, antibodies against the CRMP-5 antigen are detectable by immunofluorescence studies or Western blot (11,49). Pediatric patients with the OMS generally do not have positive paraneoplastic antibody evaluations in the serum or CSF (35). Antibodies against ANNA-2, NMDA receptor, nuclear antigens, and neuronal calcium channels have all been detected in subsets of adult patients with OMS (32,38,50,51). Antibodies against Purkinje cells may be responsible for disease pathogenesis in some patients (32). If testing is warranted, then serum, and perhaps CSF, should be sent for a full paraneoplastic evaluation that will typically use immunofluorescence for reactivity against brain and ELISA for reactivity against specific antigenic targets. In some patients, paired evaluations of antibodies in the serum and CSF are preferred (52). Given that an antibody is typically not identified, evaluation for occult malignancy is required in all patients with OMS. Patients with neuroblastoma-
associated OMS may have tumors that are small, located in the paravertebral regions, and may be challenging to identify on neuroimaging, which must be done using thin sections or ultrasound. Identification of an underlying neuroblastoma may sometimes be made on the basis of elevated catecholamine metabolites (33).

Specific testing for antibodies against the VGCC should be performed in patients who are suspected to have LEMS. These studies are generally available as ELISA tests with good specificity. Antibodies against the P/Q-type VGCC are present in 85%–90% of patients with LEMS but may also be seen in up to 4% of patients with small cell lung cancer in the absence of neurologic disease. In addition, LEMS patients may have antibodies against N-type VGCC (in up to 30%–40%) or L-type VGCC (in up to 25%) (35).

What Systemic Evaluation Should Be Performed for an Occult Malignancy?

CT of the chest, abdomen, and pelvis are essential. Breast examination and mammography should be performed. Pelvic and abdominal CT may reveal many other cancers that are associated with CAR, and pelvic examination, prostate examination, and colonoscopy should be considered in the appropriate patients. Serologic testing for specific cancer markers may also have a role in the evaluation. These tests are best ordered through a collaborative care of the patient with a hematologist–oncologist. Whole-body PET using fluorodeoxyglucose (FDG-PET) can be performed in patients in whom other testing was not revealing (53). Hematologic malignancies have been associated with the paraneoplastic syndromes, and these may require special testing including serum protein electrophoresis and bone marrow biopsy.

Management

A common thread among all of the paraneoplastic syndromes is that treatment of the underlying malignancy may be beneficial to the neuro-ophthalmological symptoms and signs. Immunologic treatment targeting the antibody-mediated paraneoplastic syndrome and symptomatic therapy also are of benefit. In addition to cytoreduction of tumor, the mainstay for treatment for CAR is use of oral or intravenous corticosteroids or a combinatorial therapy of cyclosporine, azathioprine, and prednisone with a reported response rate of up to 70% (54). Newer therapies have included rituximab (55).

Many types of treatments have been used with variable success in MAR. In general, corticosteroids are of little benefit, whereas intravenous immunoglobulin (IVIg) alone or in combination with cytoreduction of tumor burden has proven more effective (22). Successful treatment also has been reported with combination therapy such as oral prednisone, plasmapheresis, azathioprine, and gabapentin or the combination of intravenous steroids with plasmapheresis. The total number of affected patients with MAR is small and, therefore, best practice is not yet determined for these patients. BDUMP also is rare, but there have been reports of improvement with plasma exchange with or without systemic corticosteroids (56). In some cases of PON, use of intravitreal triamcinolone was associated with improvement in vision (57).

In OMS, adult patients generally respond favorably to immunotherapy treatment with intravenous corticosteroids and/or IVIg (35) in addition to the treatment of the primary tumor (surgery, chemotherapy, radiation). A wide variety of other agents have been used for symptomatic control in small numbers of patients with some success, including clonazepam, valproic acid, or gabapentin (35). Many pediatric patients with this syndrome demonstrate long-term neuropsychological morbidity, but this is believed to be ameliorated by early immunosuppressive therapy (58). A multicenter clinical trial is currently in progress to try to provide evidence-based therapeutic recommendations for OMS in pediatric patients (ClinicalTrials.gov Identifier: NCT01868269).

Suggested therapy for LEMS includes 3,4-diaminopyridine, IVIg, plasma exchange, steroids, and immunosuppressive agents (59–62). According to a Cochrane publication that reviewed trials through 2010, there is good evidence for the use of 3,4-diaminopyridine, an agent that increases the release of acetylcholine, and a single trial that demonstrated benefit from IVIg (59). The use of corticosteroids and azathioprine in addition to 3,4-diaminopyridine may be beneficial, but this is not based on prospective clinical trials (61). A new calcium channel agonist, with selectivity for both the N-type and P/Q-type VGCC, was used in an experimental model of LEMS, with promising results (62). If these results can be replicated in humans, then this would give an additional therapeutic option.

In conclusion, the paraneoplastic disorders in neuro-ophthalmology may predate identification of a malignancy. These patients require careful discussion about the possibility of an underlying disease such as cancer and also will require periodic follow-up. Treatment consists of control of tumor itself followed by symptomatic relief and use of immunosuppressant and immunomodulatory drugs.

REFERENCES


Ataxia at the Masquerade Ball

Krista Kinard, MD, Anne G. Osborn, MD, Cheryl A. Palmer, MD, Judith E. A. Warner, MD, Bradley J. Katz, MD, PhD, Alison V. Crum, MD, L. Dana DeWitt, MD, Joshua A. Sonnen, MD, Kathleen B. Digre, MD

Dr. Kinard:

Five years previously, a 52-year-old man developed diplopia requiring prism glasses. This was followed by imbalance resulting in frequent backward falls as well as oscillopsia and episodic vertigo. Subsequently, he developed fatigue, dysarthria, weight loss, numbness of his right foot, and easy bruising. He had complaints of cognitive decline but formal neuropsychological testing was normal. He had had 1 previous neurology consult and brain magnetic resonance imaging (MRI) without an explanation for his symptoms. His medical history consisted of hypertension, viral pericarditis, mononucleosis, hepatitis, and treated prostate and squamous cell skin cancers. His only medications were over-the-counter supplements. His father had undiagnosed balance problems.

At the time of initial evaluation, he reported progressive worsening of his balance. Visual acuity was normal as was examination of the anterior and posterior segment of each eye. His fixation was interrupted by intermittent square-wave jerks, and his eye movements were abnormal, with saccadic pursuit, slowed adducting saccades, gaze-evoked torsional-downbeat nystagmus, and minor bilateral abduction deficits with an esodeviation in both right and left gazes. He was unable to suppress his vestibular-ocular reflex. His neurologic examination showed normal cranial nerves and normal strength, but he had mild dysarthria, a wide-based ataxic gait, unsteady tandem walk, appendicular dysmetria, absent ankle reflexes, and decreased peripheral sensation in his feet.

His workup revealed normal nerve conduction studies, but brainstem auditory evoked responses showed delays in waves 3 and 5. Evaluation of his swallowing showed mild dysphagia with intermittent delay of pharyngeal response. MRI demonstrated only white matter disease consistent with microvascular ischemia, which was unchanged from previous studies. The following laboratory studies were normal or negative: complete blood count with differential, erythrocyte sedimentation rate, comprehensive metabolic panel, thyroid stimulating hormone, thyroxine, vitamins B1, B12, D, and E, serum protein electrophoresis/immunoelectrophoresis, mercury, arsenic, and cadmium levels, urine protein electrophoresis, antinuclear antibody (ANA) assay, Bartonella henselae, Bartonella quintana, Lyme disease, rapid plasma reagin, fluorescent treponemal antibody absorption, Mycoplasma pneumoniae, antineutrophil cytoplasmic antibodies (ANCA) titers, Toxoplasma, Anti-Ro(SSA) and Anti-La(SSB), Coxiella burnetii, acid-fast bacilli, Mycobacterium tuberculosis antibody, quantiferon gold, Trypanosoma whipplei, hepatitis C virus (HCV), herpes simplex virus (HSV), anti-JC virus (JCV) antibodies, Rocky Mountain spotted fever, varicella-zoster virus (VZV), HIV-1, HIV-2, and Epstein–Barr virus. He had a low absolute CD4 count with a low CD4:CD8 ratio, normal anticardiolipin IgG but high anti-cardiolipin IgM, high parvovirus B19 IgG but normal IgM, and normal cerebrospinal fluid (CSF) studies except for high HSV IgG. CSF cytology revealed no malignant cells. He had an unremarkable whole-body bone scan as well as negative findings on computed tomography of chest, abdomen, and pelvis. A subsequent sleep study confirmed sleep apnea for which he was placed on continuous positive airway pressure treatment. He was also evaluated at the cerebellar ataxia clinic and diagnosed with familial spinocerebellar ataxia as the most likely etiology of his symptoms. He was offered genetic testing but declined due to cost. He was placed on acetazolamide and then memantine without improvement. Over the next 6 years, his symptoms worsened despite physical and occupational therapy. He became disabled and wheelchair bound. Due to progressive decline, he had repeat MRI of the brain.

Dr. Osborn:

MRI shows multiple enhancing hyperintense foci and areas of linear enhancement (Fig. 1). When the MRI obtained 6 years earlier was reviewed, it was clear that similar foci were present at that time (Fig. 2).
Dr. Kinard:
The differential with this new information included infiltrative processes such as sarcoidosis, lymphomatoid granulomatosis, intravascular lymphoma, metastases, and infection. Repeat laboratory studies and lumbar puncture were performed and were negative or normal except for elevated CSF protein on a repeat lumbar puncture. A biopsy of the right frontal leptomeninges and brain biopsy were performed.

Dr. Palmer:
The biopsy specimen shows fibrotic leptomeninges with hyperplastic meningothelial cells and psammoma body deposition. The right frontal neocortex demonstrates multifocal perivascular and intramural chronic inflammatory cells, and diffuse astrogliosis (Fig. 3). Neither granulomas nor giant cells are seen. Trichrome staining confirmed vascular wall destruction and transmural inflammation. Immunohistochemistry is negative for cytomegalovirus and VZV. Immunohistochemical staining also shows predominantly CD3-positive T lymphocytes (Fig. 4A) with occasional CD20-positive B lymphocytes. A CD68 stain demonstrates activated micogliosis in the neocortex and transmural macrophages (Fig. 4B). These findings are diagnostic of central nervous system (CNS) vasculitis.

Dr. Kinard:
Because of the pathological diagnosis of probable CNS vasculitis, a catheter cerebral angiogram was performed to determine the extent of involvement.

Dr. Osborn:
The cerebral angiogram shows subtle irregularities of multiple distal internal carotid and vertebral artery branches consistent with vasculitis (Fig. 5). Angiography also showed normal renal and femoral arteries.

Dr. Kinard:
Laboratory studies were performed to determine if there was a specific cause for the vasculitis. These included c- and p-ANCA, ANA, and HCV, all of which were negative.

Final Diagnosis
Primary central nervous system vasculitis.

FIG. 1. Brain magnetic resonance imaging. A. Postcontrast T1 axial images show multiple areas of punctate and linear enhancement. B. Diffusion-weighted imaging reveals patchy areas of restricted diffusion.

FIG. 2. Brain magnetic resonance imaging 6 years earlier. Postcontrast T1 axial scans also show multiple foci of enhancement.
Dr. Kinard:

The patient was treated with oral prednisone (60 mg/d) with resolution of the enhancing lesions on repeat brain MRI 4 months later. Due to poor tolerance of steroids, he was started on azathioprine and tapered off of steroids. His clinical picture has improved slightly on chronic immunosuppression. He was able to go from wheelchair bound to walking with assistive devices.

Dr. Osborn:

Repeat imaging 4 months after starting steroids shows remarkable improvement. The previously noted punctate enhancement in the cerebellum is no longer present, and there is no longer any patchy diffusion restriction (Fig. 6).

Dr. Kinard:

Primary CNS vasculitis (PCNSV) is rare, usually presenting with nonspecific signs and symptoms of CNS dysfunction. Headache is the most common symptom (60%) followed by altered cognition (50%) and hemiparesis (44%). Visual abnormalities are varied and can include visual field defects and persistent or intermittent diplopia (1). Other findings include vertigo, dysarthria, and fever. There is no sex predilection. The incidence is 2.4/1,000,000 people. The etiology is unknown and without pathologic confirmation. Thus, PCNSV is a diagnosis of exclusion (1). The cause of PCNSV is unknown but theories implicate infectious diseases causing vasculitis, a specific immune response to an antigen (as yet unknown) and an association with amyloid angiopathy (1).

There are 3 histopathologic presentations of PCNSV: granulomatous, necrotizing, and lymphocytic (1). Granulomatous is the most common, and 50% of patients with this pathology also have amyloid deposition in affected vessels. The necrotizing variant is the least common. Necrotizing and granulomatous forms occasionally coexist. Our patient suffered from lymphocytic infiltration, which occurs more frequently in children than in adults.

There are no validated diagnostic criteria for PCNSV. Angiography may be helpful when abnormal, but it has limited sensitivity (2). Brain biopsy has strong negative and positive predictive values and is considered the gold standard (2). A negative biopsy does not exclude the diagnosis, so often a targeted biopsy is needed. This has a 78% diagnosis rate, as opposed to a 53%–55% diagnosis rate for a nontargeted biopsy (1).

Treatment for PCNSV usually involves administration of steroids; but, despite treatment, PCNSV has a high mortality due to complications such as cerebral infarcts (2,3). There have been no prospective clinical treatment trials due to the rarity of the condition; however, a series from the Mayo Clinic described 101 patients with PCNSV who were followed for an average of 13 months and reported that 81% responded favorably to corticosteroids. However, the patients still had an increased mortality despite treatment and approximately one-quarter had a clinical relapse during the period of follow-up (3).
Pizzanelli et al (4) reported a series of 8 patients with PCNSV that was classified as either moderate or severe. The patients classified as having moderate disease were treated with steroids, whereas patients with severe disease were treated with steroids plus additional forms of immunosuppression. The patients were followed for 7–62 months, during which 1 patient experienced a relapse. The authors concluded that brain biopsy and angiography are helpful for diagnosis and that treatment should be tailored to the patient’s clinical picture until diagnostic and therapeutic guidelines are developed.

PCNSV has long been thought to be an acute or rapidly progressive illness (2). However, Burrows et al (5) published a case report of a patient with headache and cognitive decline for 20 years, culminating with seizures. He underwent a brain biopsy that demonstrated PCNSV and was treated with steroids and lamotrigine. His seizures and apraxia resolved, and his cognitive deficits and a left homonymous hemianopia stabilized. That report and our case suggest that PCNSV may be indolent or slowly progressive over many years.

The diagnosis of vasculitis in our patient was obscured by the patient’s predominant signs and symptoms that mimicked or masqueraded as a spinocerebellar ataxia (SCA) syndrome, including a vague family history of imbalance; however, the rate of decline in our patient was faster than is typically seen in SCA. Our report highlights that PCNSV can be an insidious very slowly progressive disease. MRI findings can be subtle and nonspecific, mimicking a variety of entities and cerebral angiography, at times in conjunction with brain biopsy, provide the best possible means of diagnosis.

REFERENCES
Should Visual Restoration Therapy be Used in Patients With Visual Field Loss?

Neil R. Miller, MD, Prem S. Subramanian, MD, PhD

Visual field loss, and homonymous hemianopia in particular, results in major morbidity by causing impaired mobility and reading (1). Treatment options are limited, and few if any such therapies are supported by high-quality evidence. Visual restoration therapy is thought to expand the impaired hemi-field and result in functional recovery, but the reputed benefit is controversial. Two experts debate the use of vision restoration therapy in patients with visual field loss.

Pro: Visual Restoration Therapy: Prem S. Subramanian, MD

Vision restoration therapy is designed to improve or restore function in the damaged hemifield through stimulation of remaining viable neuronal tissue in the affected cerebral cortex (2), redirection of the visual processing through alternate pathways that arise through neuroplasticity (3), or a combination of these processes. Evidence for neuroplasticity has been obtained from animal studies showing recovery of visual field loss after visual deprivation in young (4) and adult animals (5–7), and these experiments, in part, generated initial and continuing interest in human visual field restoration. Using a suprathreshold flickering threshold, Sabel and colleagues devised a computer-based method to map and then stimulate the border zone of visual field defects, where improvement through retraining was most likely to occur. They published the first clinical study of vision restoration therapy in patients with either optic nerve-based or retrochiasmal visual field loss (8). This initial report demonstrated some effectiveness (30% of patients improving) for the retrochiasmal lesions but even greater improvement in patients with optic nerve disease (72% improved). Their work led to development of a commercially available vision restoration therapy system (NovaVision, Boca Raton, FL), and many practitioners adopted the technology to treat a cohort of patients in whom options were generally limited to compensatory strategies rather than methods to improve lost function. This training was time consuming and often expensive for patients because costs were not covered by U.S. health insurance.

Nonetheless, promising results were reported in published case series, and the majority of patients reported subjective improvement after therapy (9–11). Controversy then arose over the use of vision restoration therapy because of concerns that binocular training and testing may induce fixation artifacts or vergence movements that could be perceived as visual field improvement. Indeed, small case series of patients treated with various flickering stimulus regimens seemed to show that responses in the nonseeing field were not improved when fixation was monitored by methods different from those used in NovaVision vision restoration therapy (12).

Despite these findings, researchers continued to explore the possibilities for restorative rather than compensatory training, and techniques that combine 2 or more stimulation modalities have shown therapeutic promise. Das and Huxlin (13) used a combined method of static and kinetic stimuli in patients with homonymous field defects and have reported more accurate and reproducible target detection in patients treated with dual stimulation rather than a static target alone. Research continues into determining the precise pathway by which this recovery is mediated (restored function within the damaged visual cortex vs recruitment of extrastriate visual pathways implicated in "blindsight"). Similarly, vision restoration therapy combined with transcranial direct current stimulation (tDCS) was found to be superior to vision restoration therapy alone, with changes on functional magnetic resonance imaging correlating with the clinically measured visual field recovery (14), and the improvement was more likely to persist after the training was concluded when compared with sham tDCS and vision restoration therapy.

Application of vision restoration therapy to prechiasmal disease also has shown renewed promise with a randomized controlled trial conducted in a cohort of glaucoma patients who underwent monocular vision restoration therapy or placebo stimulation in the intact field daily for 3 months (15). The vision restoration therapy group showed significant improvement on high-resolution perimetry with gaze tracking to control for fixation, and health-related quality of life improved in this group as well.

Patients with visual field deficits face potential loss of occupation, mobility, and social interaction. Because they...
may not have other physical disabilities, they may not receive the same societal recognition of their disability, and even eye care professionals may not appreciate the impact of visual field loss in patients who retain good Snellen visual acuity. Compensatory training, while important and often beneficial, is not intended to take advantage of the potential visual function that may be present in our patients. The value of early and aggressive rehabilitative therapy in motor stroke is well proven, and to deny our patients, the opportunity to recover visual function from damaged but viable areas of cortex would not seem appropriate.

### Point Counter-Point

**Con: Visual Restoration Therapy Should Not Be Used In Patients With Visual Field Loss:**  
**Neil R. Miller, MD**

Vision restoration therapy is based on the belief that there is some degree of plasticity in the central nervous system, even in adults. The theory is that visual neurons in the brain (e.g., in the occipital lobe) adjacent to an area of damage (e.g., from stroke, trauma) that are alive but not functioning normally may be induced to function normally again or may take over the role of the dead adjacent neurons. Although several publications have suggested that vision restoration therapy can improve the visual field in patients with homonymous hemianopia and, in doing so, improve a patient’s ability to perform his/her daily activities and quality of life (9,16–18), there are a number of issues that should make one question these claims. First, some of the patients were assessed shortly after the onset of their visual field loss. Zhang et al (19) showed that many patients with homonymous field defects improve, usually within 3 months from onset. Thus, patients who begin vision restoration therapy shortly after developing a homonymous field defect and subsequently show definite improvement may have improved without vision restoration therapy. Second, it is bothersome that patient reports of subjective improvement in daily activities after a 6-month course of vision restoration therapy do not correlate with visual field improvement. Some patients with apparent improvement in their visual field report no improvement in any daily activities, whereas others with no improvement in their visual field report improvement in one or more daily activities. Third, there is compelling evidence from Reinhard et al (12) that the apparent improvement in the field of patients with homonymous hemianopias who undergo vision restoration therapy is due not to expansion of the field but to micro eye movements. These investigators assessed 17 patients with homonymous hemianopia before and after vision restoration therapy using a scanning laser ophthalmoscope to monitor fixation. They found that no patients with steady fixation showed clear-cut visual field expansion. Finally, Roth et al (20) performed a randomized controlled study comparing objective and subjective results before and after flicker training (FT). These investigators used software that generated flickering letters in areas on either side of the vertical midline with equal times in blind and seeing hemifields. The patients were instructed to fixate centrally on a vertically aligned panel with letters and had to click the mouse within 10 seconds on the panel letter that was flickering. They found that FT produced no objective or subjective effects on the visual fields of any subjects tested.

In the final analysis, vision restoration therapy is not harmful to a patient with an homonymous field defect, and if it were free or the cost were minimal, it would not be an unreasonable therapy as it might very well improve visual attention or, at the very least, provide a positive placebo effect; however, the cost of vision restoration therapy would seem to be excessive for what it provides to the patient. I believe that straight-forward techniques to improve visual attention and use of the patient’s existing field are preferable to vision restoration therapy.

**Rebuttal: Prem S. Subramanian, MD**

Dr. Miller raises 2 major criticisms of vision restoration therapy. He suggests that it is not appropriate to start vision restoration therapy at an early time point because some individuals may recover function spontaneously in the first 6 months after vision loss. He also describes a number of alternative methods for helping patients with visual field loss, all of which rely on compensatory strategies and make no effort to improve detection of stimuli within the damaged visual field, and states that they are effective and less expensive than vision restoration therapy. Ideally, a randomized, double-masked, placebo-controlled prospective clinical trial of vision restoration therapy might establish early intervention as the preferred method. Significant barriers including cost and difficulty in obtaining a matched subject population across multiple centers make such a trial challenging.

In the absence of these data, we must rely on findings from other neurological syndromes and what is known about treatment. In reviewing the stroke literature, it becomes evident that if neurological function is to be restored and not just compensated for, then the treatment regimen must be instituted early. Animal models have
shown that early intervention leads both to reorganization of function in the intact uninjured cortex and to improved preservation and recovery of function in the injured brain. Rats exposed to a stimulating environment and reach training were found to upregulate expression of FosB/FosB, a marker of use-dependent neuronal activity in perilesional cortex (21). Uninjured animals had no change in gene expression when provided with identical treatment, nor did animals exposed only to either the enriched environment or reach training alone. These data provide additional support for the development of strategies that combine complementary rehabilitation methods and may explain in part the seemingly modest and sometimes insignificant improvement observed with single intervention methodology.

While it is true that some patients with homonymous hemianopia will experience spontaneous visual field recovery within the first 6 months, it is precisely during that period that the maximal potential for interventional treatment exists. The AVERT (A Very Early Rehabilitation Trial) protocol, which is designed to investigate return of motor function in hospitalized acute stroke patients, engages patients in active therapy within 24 hours of symptom onset. Even patients treated with thrombolytic agents are eligible. The study is currently in Phase III, but Phase II data demonstrated a statistically significant improvement in return to walking in the treated group when compared with standard stroke rehabilitation therapy (22). A large randomized trial in China of patients with hemorrhagic stroke, where outcomes are usually poor, showed that active rehabilitation within 48 hours was associated with markedly reduced mortality at 6 months (a 4-fold difference between the groups) and improved quality of life in survivors compared with patients who underwent standard therapy (23).

Compensatory training including saccadic tasks, reading guides, high-power monocular or binocular sector prisms, and even patient-directed natural recovery all do result in improved visual and overall functioning. However, by definition, they are designed to help those patients in whom recovery of visual field is not expected. This is a laudable goal, and I do not take issue with the benefit of such methods. That does not mean that we cannot and should not also develop alternate treatment strategies for our patients. We must be willing to identify and enroll patients in well-designed clinical trials that provide early intervention and overcome our tendency to wait for spontaneous recovery and then rehabilitate only the patients who continue to have visual deficits. The data from our stroke patients and their counterparts in the laboratory are compelling, and we must not allow our patients to be captives of the natural history of their debilitating disease.

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**Rebuttal: Neil R. Miller, MD**

I agree with Dr. Subramanian that, in general, the earlier one intervenes after an acute neurological deficit, the more likely it is that the patient will recover at least some function. In addition, there certainly is no physical or mental harm in early intervention, even if the patient would have improved without it. I also agree that, at least by functional imaging, the adult brain is, to some degree, capable of rewiring. Finally, I agree that our goal should be to expand the nonseeing field in patients with homonymous hemianopia.

Having said this, I think he and I would agree that the perfect treatment for patients with homonymous hemianopia does not yet exist and that there are alternatives to vision restoration therapy that are far less expensive. They mainly relate to improving use of the existing field. First, many patients with homonymous hemianopia learn to use their remaining visual field quite effectively on their own. Unless the patient has associated visual inattention or other neurological deficits, he or she may be able to perform most daily activities without intervention. For patients with left homonymous hemianopia, a “reading screen” can be used. This is a black screen with an adjustable opening that helps patients find the beginning of each line. The same benefit can be achieved with a ruler or other straight-edged object positioned under each line of text or placing a finger at the left edge of text (24) and using proprioception to determine where the next line of text begins. For patients with right homonymous hemianopia, there is an “inversion telescope” that enables patients to read from right to left rather than left to right (25), although the same benefit can be achieved by having the patient place a finger at the right edge of text, again using proprioception to determine where the text ends.

As far as improving use of the existing field is concerned, it has been shown by several investigators that saccadic visual search training can be useful (20,24). In particular, Roth et al (20) assessed the usefulness of explorative saccade training (EST). These investigators used a laptop computer with a software program that generated a random array of digits (0–9, 12-point Arial font) that were distributed with equal probability on blind and seeing sides. The patient had to move the cursor over a predefined digit. Once the cursor passed over the correct digit, the program generated a sound (“beep”) and the digit turned to a red “$.” These investigators found that EST improved saccadic behavior, natural search, and scene exploration on the blind side associated with subjective improvement in activities of daily living. Finally, Fresnel prisms have been used to expand the existing field. There are several options. Option 1 is to place a 30-prism diopter prism base out on the outside half of a spectacle lens on the side of the hemianopia. This is difficult for patients because the prism has no effect in
primary gaze or when gaze is shifted toward the seeing hemifield. The prism induces pericentral field loss (apical scotoma) when gaze is shifted into it. The second option is for 15- or 20-prism diopter prisms to be placed base out on the spectacle lens on the side of the hemianopia and base in on the contralateral lens. These prisms have an effect only when gaze is directed into prism and may cause apical scotoma, diplopia, or both. The final option, which is the best as far as I am concerned, is to use monocular sector prisms. These prisms are effective at all gaze angles (26,27).

In summary, I am hopeful that someday, we will have a method of expanding the hemianopic field that not only truly is useful but also is inexpensive. Until then, we are stuck with our current techniques, imperfect as they are.

CONCLUSIONS

Vision restoration therapy may be effective for select patients, but identifying patients who might benefit remains challenging, particularly given the time and expense of treatment. The treatments available for visual field loss are supported by studies that are often hampered by the lack of a control group and reliance on subjective end points that may or may not translate into real-world visual function. A large placebo-controlled treatment trial with objective clinical end points would provide greater support for routine use of vision restoration therapy in this patient population. For the time being, vision restoration therapy will likely remain one choice among many for patients with visual field loss.

REFERENCES

Literature Commentary


Background: Leber’s hereditary optic neuropathy (LHON) and a multiple sclerosis (MS)–like illness appear to coexist 50 times more frequently than would be expected by chance. This association of LHON and MS (LMS) raises an important question about whether there could be a common pathophysiological mechanism involving mitochondrial dysfunction.

Objective: The primary aim was to define magnetic resonance imaging (MRI) features of LMS and LHON and to assess the proportions of individuals displaying features typical of MS. Secondarily, we investigated the effect of gender on the risk of developing white matter lesions in the context of LHON.

Methods: A blinded standardized review of conventional brain MRIs of 30 patients with MS, 31 patients with LHON, and 11 patients with LMS was conducted by 3 independent experts in the field. MS-like MRI features were assessed.

Results: All patients with LMS and 26% of patients with LHON had white matter lesions. Of these, all patients with LMS and 25% with LHON were found to have an MRI appearance typical of MS. Female patients with LHON had a significantly greater risk of having white matter lesions, consistent with MS compared with male patients (relative risk 8.3).

Conclusions: A blinded review of conventional brain MRIs shows that patients with LMS have a scan appearance indistinguishable from MS. Mitochondrial dysfunction could be a common pathophysiological pathway in the formation of white matter lesions. There appears to be a strong female influence on the radiological appearance and clinical development of MS in patients with LHON.

In this observational, retrospective, brain magnetic resonance imaging (MRI) study totaling 72 patients, 3 neuroradiology experts performed a blinded analysis on 3 set of patients: MS (n = 30), LHON (n = 31), and LMS (i.e., Harding syndrome) (n = 11).

There were several intriguing findings in this study. First, in terms of general numbers,

1. Of the 12 women with either LHON or LMS, 4 had LHON and 8 had LMS.
2. Of the 30 men with either LHON or LMS, 27 had LHON and 3 had LMS.
3. Of the 4 women with LHON, 3 (75%) had asymptomatic T2 hyperintense white matter lesions; and
4. Of the 27 men with LHON, 5 (18.5%) had asymptomatic T2 hyperintense white matter lesions.

Even though male patients with the LHON genetic mutation had a greater chance of phenotypic expression than female patients with the same LHON genetic mutation, in this study, there were more female patients with LMS (n = 8) than male patients (n = 4). The calculated relative risk of a LHON woman having cerebral white matters lesions was 8.3 (95% confidence interval, 2.8–25.1; P < 0.01).

In the discussion, the authors highlighted the fact that there is growing evidence that mitochondrial dysfunction plays an important role in the pathophysiology of MS, and of course, there is no debate that mitochondrial dysfunction is the primary factor in the loss of vision in patients with LHON.

This study adds to the body of evidence that the association of MS and LHON is more than coincidental and that there is a plausible scientific explanation for the
MS-like illness that is seen is some patients with LHON. One of the questions that remains unknown is the risk of developing MS in a patient with LHON and asymptomatic white matter lesions on MRI.

—M. Tariq Bhatti, MD

I would agree with most of what you say. However, your love of LHON and MS overlap, notwithstanding I don’t think we know for sure that the incidence of this overlap syndrome is more than a chance occurrence of a common disease (MS) in a population with LHON. Other reports (2) have suggested this, and one would expect a more frequent diagnosis of MS by MRI or clinical criteria in a population who already presented with severe visual loss.

—Mark L. Moster, MD

REFERENCES


Objective: To define the efficacy, safety, and cost-effectiveness of a single center approach to evaluating Horner syndrome (HS) including a simplified single neuroimaging protocol.

Design: Case series study.

Participants: Medical records of 34 patients diagnosed with HS at the Houston Methodist Hospital (HMH) were reviewed after obtaining institutional review board approval.

Methods: A retrospective chart review was performed for all patients presenting with the diagnosis of HS at the HMH from January 2010 to November 2013. All patients had diagnostic imaging with contrast-enhanced brain magnetic resonance imaging (MRI) extending to the T2 level in the chest. They either had documented causative diagnosis for HS or were “idiopathic.” Efficacy and cost-effectiveness of the proposed neuroimaging technique were analyzed and compared with other recommended protocols.

Results: We initially reviewed 34 charts with presumed diagnosis of HS; 27 charts were included in the analysis. The average age of patients was 46.6 years. Eleven patients (41%) had a final diagnosis of HS secondary to a proven cause, and 16 patients (59%) were diagnosed as “idiopathic.” Ten patients (63%) in the idiopathic group had follow-up, and none of those with follow-up had an alternative cause. The estimated cost of our recommended MRI protocol was US $667.76 without magnetic resonance angiography (MRA) or US $1501.71 with MRA.

Conclusions: A single contrast-enhanced brain MRI extending to the T2 level in the chest is an effective and simple means of ruling out life-threatening and other causative factors of HS. Compared with previous imaging recommendations, this proposed protocol may be simpler for clinicians to use and more cost-effective.

The authors describe their approach to evaluating patients with non-localizable, isolated HS, noting that prior literature has proposed various different approaches. They use standard clinical criteria, selective use of apraclonidine, and then imaging with magnetic resonance imaging (MRI) extending from the brain to the T2 spinal cord level and a magnetic resonance angiography (MRA) of the neck. They find the approach to be effective and lower cost than many others. As the authors note, there are limitations to this study, including not knowing the true cost of studies (they used Medicare reimbursement rates), a small number of patients, limited follow-up, and retrospective data collection.

So why review this article? As the subspecialty with the most expertise in HS, I think we have to come up with the best way to evaluate these patients and propose some changes to our radiology departments, institutions, and insurance companies. With this in mind, I think the authors approach makes a lot of sense.

Currently, what I order on patients with no-localizable, isolated HS depends on which office I see them in (Wills Eye vs suburban Philadelphia vs south New Jersey), at which institution they are studied, and what insurance they have. The orders might include a combination of the following: MRI brain, MRI neck, MRI chest, MRA neck, CT brain, CT neck, CT chest, or computed tomographic angiography (CTA). Sometimes, the decision of what to obtain depends on my conversation with the medical reviewer at the insurance company. Even so, occasionally, I am not confident that I’ve adequately imaged the entire oculosympathetic pathway.

If we can come up with an agreed upon guidelines along the lines recommended in this article, perhaps in partnership with the American Academy of Neurology or the American Academy of Ophthalmology, we can get appropriate imaging, easier insurance approvals, and not have to order up to 4 different studies. Additionally, when I’ve seen patients who have been evaluated by neurologists or ophthalmologists, often a portion of the oculosympathetic pathway has been overlooked. Since many or most HS patients don’t make it to a neuro-ophthalmologist, a simplified recommendation, such as proposed here, will lead to a more appropriate evaluation.

As the authors note, their protocol is likely faster to perform, simpler for clinicians to order, less costly, and adequately assesses all areas of concern in patients with HS.

—Mark L. Moster, MD

I agree with you, Mark, that it is very important for specific guidelines to be developed to aid clinicians in evaluating patients with common disorders, such as HS. However, a step further in the process would be to develop “standard-of-care” protocols that can be accepted universally in both the medical and legal communities.
I was happy to see this article because it very much parallels the neuroimaging protocol that we developed here at the Duke University Medical Center with the neuroradiology service, which is a contrasted MRI from the head to the upper chest and cervical MRA. My pharmacological strategy for HS is exactly the same as the authors, which is to confirm the diagnosis of HS with apraclonidine (sometimes cocaine) but not to perform the hydroxyamphetamine test. As an aside, I found it very interesting that 59% of the patients evaluated were found to have idiopathic HS. What this study does not answer is whether MRI/MRA is better than CT/CTA in the evaluation of a patient with HS.

—M. Tariq Bhatti, MD


Abstract: We retrospectively evaluated predictors of conversion to multiple sclerosis (MS) in 357 children with isolated optic neuritis (ON) as a first demyelinating event who had a median follow-up of 4.0 years. Multiple Cox proportional hazard regressions revealed abnormal cranial magnet resonance imaging (cMRI; hazard ratio [HR], 5.94; 95% confidence interval [CI], 3.39–10.39; P < 0.001), presence of cerebrospinal fluid oligoclonal IgG bands (OCB; HR, 3.69; 95% CI, 2.32–5.86; P < 0.001), and age (HR, 1.08 per year of age; 95% CI, 1.02–1.13; P = 0.003) as independent predictors of conversion, while sex or laterality (uni- vs bilateral) had no influence. Combined cMRI and OCB positivity indicated a 26.84-fold higher HR for developing MS compared to double negativity (95% CI, 12.26–58.74; P < 0.001). Accordingly, cerebrospinal fluid analysis may supplement cMRI to determine the risk of MS in children with isolated ON.

Despite the urge to consider pediatric optic neuritis as a form of adult optic neuritis, it is evident that these 2 entities are quite different from each other in terms of clinical presentation, underlying etiologies, visual outcome, and neurological implications (i.e., risk of developing multiple sclerosis [MS]). The Optic Neuritis Treatment Trial (ONTT) was a prospective clinical trial that enrolled 457 patients between the ages of 18 and 46 years with optic neuritis. The ONTT found that the presence of oligoclonal bands (OCB) was not helpful in predicting the future development of clinically definite multiple sclerosis in patients with an abnormal magnetic resonance imaging (MRI) (1).

Heussinger et al report the results of a retrospective, multicenter (27 hospitals) study that included 357 children (<18 y of age) with optic neuritis to determine the prognostic indicators for the conversion to McDonald criteria MS. A sophisticated statistical analysis was performed using both simple and multiple Cox proportional hazard regressions, and 2 multiple regression analysis models (one model that used the MRI and OCB as binary covariates and the other model that used MRI and OCB as categorical variables) were generated. The regression analysis was done in bootstraps of 1000 repetitions (which I must admit I do not know much about) that does not make any statistical assumptions and allows for more precise confidence intervals and P values.

Based on a median follow-up of 4 years, 40.6% of the patient cohort developed CDMS and 1.4% developed neuromyelitis optica (NMO). The univariate and multivariate analysis found higher age, abnormal MRI, and presence of OCB predictors for the future development of MS. The presence of an abnormal MRI and OCB had a higher predictive value than each factor alone. Gender and optic neuritis laterality were not predictive factors in the future development of MS. Finally, the authors provided the 4-year conversion risk of MS in all the patients (n = 291) who had a minimum of 4 years of follow-up. The table below summarizes those results.

I was struck by the high conversion rate of pediatric optic neuritis to MS. In addition, even though OCB status is helpful in predicting the future development of MS, cranial MRI (cMRI) is the major driving force for predicting the conversion to MS (nearly 50% of patients with a positive cMRI and negative OCB developed MS compared to only 35% of patients with a negative cMRI and positive OCB). The ultimate goal of a study like this is to try to determine as accurately and quickly as possible those patients who will go on to develop MS and institute disease modifying drugs (DMD). I think it is important to understand that the treatment of a clinically isolated syndrome (i.e., optic neuritis) with a DMD is based on prospective clinical trials that enrolled patients with an abnormal cMRI. To my knowledge, there is no clinical trial assessing the value of initiating DMD therapy in a patient with clinically isolated syndrome and a normal cMRI. Therefore, I would not recommend DMD therapy in

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<td>cMRI positive</td>
<td>49% (18/37)</td>
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<td>cMRI negative</td>
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a patient with optic neuritis, normal cMRI, and positive OCB. As a result, in most cases (unless I am concerned about an alternative diagnosis), I don’t perform a lumbar puncture to determine the future risk of MS based on the OCB status in an adult patient with normal cMRI and I would argue to extend this strategy to children as well.

A prospective clinical trial similar to the adult ONTT is needed to establish a level-1 evidence–based approach to the management of pediatric optic neuritis. It is my understanding that Dr Grant Liu at the University of Philadelphia and Dr Stacy Pinedes at the University of California at Los Angeles are organizing a pilot study (pediatric optic neuritis treatment trial). I think that such a study is desperately needed.

—M. Tariq Bhatti, MD

There are a few issues that I have with this report. First, one of the reasons for the high rate of conversion to MS in this study compared to older studies is that the criteria for developing MS were McDonald criteria, allowing for the diagnosis of MS based on MRI demonstration of dissemination in time and space and not requiring a second clinical event. An additional possible source of bias may be that 52% of those who developed MS were treated with immunomodulatory agents when they initially presented with MS. In this nonstandardized, retrospective study, I have little doubt that those treated with MS medications were watched more carefully, had MRI scans more frequently, and likely had their MRI more carefully scrutinized by the pediatric neurologists who interpreted the scans (neuroradiologists were not used in this study). Another source of bias was the exclusion of any child followed for less than 2 years who did not develop MS but the inclusion of those who did go on to develop MS.

Another surprising finding is that 69.7% of those developing MS did so within 1 year. One wonders whether the MRI findings seen at follow-up really occurred at the time of the optic neuritis (ON).

Despite these limitations, the data suggest that OCBs in the cerebrospinal fluid independently predict conversion to MS. With this in mind, Tariq, I’m surprised you would still not recommend lumbar puncture in children with ON. If these results are verified in future studies, it would make sense to check CSF in those children with ON with a negative MRI.

—Mark L. Moster, MD

**REFERENCE**


**Importance:** In patients with isolated optic neuritis (ON), the presence of antibodies to aquaporin 4 (AQP4) has diagnostic and prognostic value. In the same clinical setting, the significance of antibodies to myelin–oligodendrocyte glycoprotein (MOG) or the glycine receptor α1 subunit (GlyR) is unclear.

**Objectives:** To investigate the frequency of antibodies to AQP4, MOG, and GlyR in patients with unilateral or bilateral, severe, or recurrent isolated ON and to determine their clinical and prognostic correlates.

**Design, Setting, and Participants:** Retrospective case–control study from 11/1/2005, through 5/30/2015 outside the optic nerves and 142 controls (30 healthy individuals, 48 patients with neuromyelitis optica, and 64 patients with multiple sclerosis).

**Main Outcomes and Measures:** Clinicoimmunologic analysis. We determined the presence of antibodies to AQP4, MOG, and GlyR using cell-based assays.

**Results:** The median age of the patients at the onset of ON symptoms was 28 (range, 5–65) years; 36 patients (71%) were female. Antibodies were identified in 23 patients (45%), including MOG in 10 patients, AQP4 in 6 patients, and GlyR in 7 patients (concurrent with MOG in 3 and concurrent with AQP4 in 1). Patients with AQP4 antibodies (median visual score, 3.5 [range, 1–9]) had a worse visual outcome than patients with MOG antibodies alone (median visual score, 0 [range, 0–5]; P = 0.007), patients with seronegative findings (n = 28) (median visual score, 1.0 [range, 0–14]; P = 0.08), and patients with GlyR antibodies alone (n = 3) (median visual score, 0 [range, 0–2]; P = 0.10). The median age of the 7 patients with GlyR antibodies was 27 (range, 11–38) years; 5 (71%) of these were female. Among the 3 patients with GlyR antibodies alone, 1 patient had monophasic ON, 1 had recurrent isolated ON, and 1 had conversion to multiple sclerosis. The 3 patients with GlyR antibodies concurrent with MOG antibodies had recurrent isolated ON, and the patient with concurrent AQP4 antibodies had conversion to neuromyelitis optica. Of the 48 controls with neuromyelitis optica, 37 (77%) had AQP4 antibodies, 4 (8%) had MOG antibodies, 2 (4%) had AQP4 antibodies concurrent with MOG antibodies, and 5 (10%) were seronegative. Of the 64 controls with multiple sclerosis, 5 (8%) had GlyR antibodies.

**Conclusions and Relevance:** Forty-five percent of patients with unilateral or bilateral, severe, or recurrent isolated ON had antibodies to MOG, AQP4, or GlyR. Patients with AQP4 antibodies had the poorest visual outcomes, whereas patients with MOG antibodies had a better outcome that was similar to that of patients with seronegative findings. The significance of GlyR antibodies in the setting of ON is unclear and deserves further study.

This study found that the presence of antibodies to AQP4, MOG, or GlyR in 45% of patients with isolated optic neuritis (ON), which was severe and/or bilateral and/or recurrent. These patients had no clinical evidence of neurologic disease elsewhere and did not have magnetic resonance imagings that were typical for either MS or NMO. Twenty percent had MOG antibodies, 12% AQP4, and 14% GlyR. As one might expect, those with AQP4 had
Since Mark L. Moster, MD

Cerebral venous thrombosis is

M. Tariq Bhatti, MD

Our systematic review suggests that mechan-

ical thrombectomy is reasonably safe, but controlled studies are required to provide a definitive answer on its efficacy and safety in patients with cerebral venous thrombosis.

Although not very common, cerebral venous thrombosis (CVT) is an important condition for neuro-ophthalmologists to be aware of because it can mimic idiopathic intracranial hypertension. In addition, a miss or delay in diagnosis can result in a fatal outcome. The management of CVT is based on identifying the condition, determining the underlying etiology, and initiating anticoagulation therapy. Treatment in those cases that are nonresponsive to anticoagulation may require an invasive surgical or endovascular procedure.

With the systematic review, it was concluded that mechanical thrombectomy (MT) (with or without intrasinus thrombolysis) should be considered in a select group of patients with severe CVT not responsive to systemic anticoagulation. However, in those patients with impending transtentorial herniation, the authors recommended a decompressive hemicraniectomy instead of MT. The authors acknowledge many limitations of their study and also point to the disadvantages of MT, including the high cost of the procedure, technical difficulty of performing the procedure, and inherent complications of the procedure.

As noted by the authors, small case series tend to report their good outcomes and not the disasters. The authors were surprised that they found only 1 case reported of a vessel perforation. What we can conclude at this point is that in patients who are really in dire straits with CVT, in addition to intrasinus thrombolysis, MT can be considered as a last resort and may possibly improve outcome.

—Mark L. Moster, MD

I think you would agree with me, Mark, that since the identification of the autoantibody associated with NMO, our ability to make the diagnosis has been greatly enhanced and our understanding of the underlying pathophysiology substantially advanced. In addition, more and more autoantibodies are being discovered that may or may not have a direct relationship to certain disease entities. The one comment I would make regarding this study is the fact that all the patients evaluated had severe and/or bilateral and/or recurrent optic neuritis. I personally don’t order anti-AQP4 (NMO IgG) on every patient with optic neuritis, especially those with “typical” optic neuritis as defined by the Optic Neuritis Treatment Trial.

—M. Tariq Bhatti, MD


Background and Purpose: Cerebral venous thrombosis is generally treated with anticoagulation. However, some patients do not respond to medical therapy, and these might benefit from mechanical thrombectomy. The aim of this study was to gain a better understanding of the efficacy and safety of mechanical thrombectomy in patients with cerebral venous thrombosis, by performing a systematic review of the literature.

Methods: We identified studies published between January 1995 and February 2014 from PubMed and Ovid. We included all cases of cerebral venous thrombosis in whom mechanical thrombectomy was performed with or without intrasinus thrombolysis. Good outcome was defined as normal or mild neurological deficits at discharge (modified Rankin Scale, 0–2). Secondary outcome variables included periprocedural complications and recanalization rates.

Results: Our study included 42 studies (185 patients). Sixty percent of patient had a pretreatment intracerebral hemor-

rhage, and 47% were stuporous or comatose. AngioJet was the most commonly used device (40%). Intrasinus thrombolysis was used in 131 patients (71%). Overall, 155 patients (84%) had a good outcome, and 22 (12%) died. Nine patients (5%) had no recanalization, 38 (21%) had partial, and 137 (74%) had near to complete recanalization. The major periprocedural complication was new or increased intracerebral hemorrhage (10%). The use of AngioJet was associated with lower rate of complete recanalization (odds ratio, 0.2; 95% confidence interval, 0.09–0.4) and lower chance of good outcome (odds ratio, 0.5; 95% confidence interval, 0.2–1.0).

Conclusions: Our systematic review suggests that mechanical thrombectomy is reasonably safe, but controlled studies are required to provide a definitive answer on its efficacy and safety in patients with cerebral venous thrombosis.

Importance: Thyroid-associated ophthalmopathy (TAO) is a common and debilitating manifestation of Graves disease (GD). Presently, little is known about the factors that may increase the risk of developing TAO among patients with GD.

Objective: To identify the risk factors associated with the development of TAO among individuals with newly diagnosed GD.

Design, Setting, and Participants: In this longitudinal cohort study, all beneficiaries 18 years of age or older with newly diagnosed GD who were continuously enrolled in a large, nationwide, US-managed care network and who visited an eye care professional 1 or more times from 2001 to 2009 were identified. International Classification of Diseases, Ninth Revision, Clinical Modification billing codes were used to identify those who developed manifestations of TAO. Multivariable Cox regression was used to determine the hazard of developing TAO among persons with newly diagnosed GD, with adjustment for sociodemographic factors, systemic medical conditions, thyrotropin levels, and medical and surgical interventions for the management of hyperthyroidism.

Main Outcomes and Measures: Manifestations of TAO measured by hazard ratios (HRs) with 95% confidence intervals (CIs).

Results: Of 8404 patients with GD who met the inclusion criteria, 740 (8.8%) developed TAO (mean follow-up, 374 d since initial GD diagnosis). After adjustment for potential confounders, surgical thyroidectomy, alone or in combination with medical therapy, was associated with a 74% decreased hazard for TAO (adjusted HR, 0.26; 95% CI, 0.12–0.51) compared with radioactive iodine therapy alone. Statin use (for ≥60 days in the past year vs <60 d or nonuse) was associated with a 40% decreased hazard (adjusted HR, 0.60; 95% CI, 0.37–0.93). No significant association was found for the use of nonstatin cholesterol-lowering medications or cyclooxygenase 2 inhibitors and the development of TAO.

Conclusions and Relevance: If prospective studies can confirm our finding that a thyroidectomy and statin use are associated with substantially reduced hazards for TAO among patients with GD, preventive measures for this burdensome manifestation of GD may become a reality.

One of the most frustrating conditions we treat is TAO, related to the complexity of the symptoms and the limited efficacy of our treatments. Optimally, patients with GD should be treated in a way that would decrease the risk of developing TAO. This study found that 8.8% of patients who were diagnosed with GD and were followed for a mean of 374 days went on to develop TAO. Associated with a higher risk of TAO were treatment with radioactive iodine, elevated thyroid stimulating hormone, and an elevated thyroid stimulating immunoglobulin. Associated with a lower risk were treatment with thyroidectomy and use of statins.

The study has the limitation of lack of clinical information—merely using coding from a billing database. For instance, it is possible that the risk of TAO may be modified by the lipid abnormalities rather than the treatment with a statin, but lipid levels and comorbidities were not assessed. Additionally, there is no information available on smoking status in this study.

Interestingly, in addition to verifying our prior understanding of radioactive iodine increasing the risk of TAO, this study provides evidence that thyroidectomy decreases the risk. Further study is warranted to determine if thyroidectomy, statin use, and the avoidance of posttreatment elevations of thyroid stimulating hormone will result in fewer patients developing TAO.

—Mark L. Moster, MD

This is a very interesting report that emphasizes the need for more research regarding the risk factors that influence the development or worsening of TAO in patients with GD. The authors found that surgical thyroidectomy was associated with a decreased risk of developing thyroid eye disease. The literature contains a mix of results (no change, improvement, or worsening) regarding the influence of surgical thyroidectomy and its influence on TAO. Prior to this study, a meta-analysis of 3 prospective trials comparing total vs subtotal thyroidectomy found no difference between these 2 procedures in the development or worsening of TAO (1).

This study confirms what has already been well established in the literature, that radioactive iodine is associated with the progression of TAO. However, what I found intriguing was the decreased risk of TAO with statins, which has not been well studied to date. I was surprised to see that COX-2 inhibitor use had no effect on TAO.

Mark, you had mentioned the limitation of the study and I think it is worth emphasizing that the status of smoking and over-the-counter medications were not assessed, which I think are 2 very important factors that need to be analyzed. Finally, it is important to appreciate the fact that most patients with GD do not develop TAO!

—M. Tariq Bhatti, MD

REFERENCE

Letters to the Editor

Waldenstrom Macroglobulinemia Mimicking Temporal Arteritis

I read with great interest the very interesting article by Hughes et al (1) on “Isolated optic nerve, chiasm and tract involvement in Bing-Neel syndrome.” In 1985, we reported a case of a 65-year-old woman who reported sudden visual loss in one eye associated with an inferior altitudinal visual field defect and optic disc edema with peripapillary and peripheral retinal hemorrhages (2). Over the preceding months, she experienced malaise, intermittent fever, and muscle pains. Her evaluation revealed a hypochromic anemia and sedimentation rate of 122 mm/h. Although giant cell arteritis was believed to be a likely diagnosis, the findings of hepatomegaly, lymphadenopathy, a reversed albumin/globulin ratio, and an elevated serum concentration of immunoglobulin M led to a diagnosis of Waldenstrom macroglobulinemia. Despite appropriate treatment, including plasmapheresis, the patient experienced ischemic optic neuropathy in the fellow eye. The ischemic events likely were triggered by hyperviscosity due to Waldenstrom macroglobulinemia although other potential mechanisms included an autoimmune reaction or invasion of the optic nerve and brain by lymphocyttoplasmoid cells.

This case teaches us that even when facing signs and symptoms which perfectly match a likely diagnosis (giant cell arteritis in our patient), we should not close our mind to other diagnostic possibilities. Frenchmen have a saying: “En medicine comme dans l’amour Il n’y a pas de jamais il n’y a pas de toujours” (In medicine, like in love, there is not such a thing as never, there is not such a thing as always).

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The author reports no conflicts of interest.

REFERENCES

Palinopsia and Other Reversible Visual Disturbances Induced by Topiramate

We read with interest the article by Yun et al (1) describing 9 new patients with topiramate-induced palinopsia. Palinopsia, consisting of the persistence of visual images after the removal of the initial stimulus, may be observed in different medical conditions, especially migraine (2), but may also be provoked by different medications. Topiramate is an antiepileptic drug useful for migraine prophylaxis and for the treatment of both partial and generalized seizures (3). Topiramate has been rarely associated with adverse ocular events, in particular ciliochoroidal effusion syndrome, but patients with transitory visual disturbances induced by topiramate are being increasingly recognized (1). We evaluated 2 patients with other types of visual disturbances that were severe but transitory and fully reversible and appear related to beginning topiramate or dosage increase of the medication.

Patient 1: A 19-year-old woman had a 1-year history of migraine with aura. Her headaches usually were preceded by visual symptoms (teichopsia or visual distortion) lasting for about 20–30 minutes and occurred monthly. Topiramate was started at a daily dose of 25 mg. Within 5 days, she complained as if looking “through a veil.” This visual disturbance was continuous, and she was not taking any other medications. A complete ophthalmologic examination was unremarkable. Physical examination, numerous blood tests, brain magnetic resonance imaging (MRI), and electroencephalography were normal. Topiramate was discontinued, and within 2 days, her visual symptoms completely disappeared. She was prescribed amitriptyline for migraine prophylaxis. There was no recurrence of her visual symptoms in 6 years of follow-up.

Patient 2: A 21-year-old man had a 6-year history of juvenile myoclonic epilepsy. Initially, he was treated with levetiracetam 3 g/d, with reduction of seizure frequency. At age 20 years, topiramate 100 mg/d was added, and he remained seizure-free for 5 months. He then experienced 2 generalized tonic–clonic seizures, and his topiramate was gradually increased by 50 mg/wk up to 200 mg/d. Two days after reaching the maximal dosage, the patient complained of severe blurred vision (“I see all black”) that lasted for approximately 30 minutes. He had no similar symptoms in the past and was taking no other medications. Neurologic and ophthalmologic examinations were normal. Topiramate was gradually reduced to 50 mg/d and valproate was given at 1,000 mg/d. In the ensuing 9 years, he has not experienced seizures or visual disturbances.

Our 2 patients had reversible visual disturbances associated with use of topiramate. In our first patient, visual complaints began after institution of topiramate, whereas in the second patient, visual symptoms were associated with an increase in the dose of medication. Either discontinuing the medication (patient 1) or lowering the dose (patient 2) led to
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Our 2 patients had reversible visual disturbances associated with use of topiramate. In our first patient, visual complaints began after institution of topiramate, whereas in the second patient, visual symptoms were associated with an increase in the dose of medication. Either discontinuing the medication (patient 1) or lowering the dose (patient 2) led to
cessation of the visual disturbances. The symptoms experienced by our patients expand the spectrum of visual complaints experienced by patients taking topiramate.

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REFERENCES

Asymmetric Papilledema in Idiopathic Intracranial Hypertension: Comment

We would like to congratulate Bidot et al (1) for their article on asymmetric papilledema. Their study is the first to demonstrate a morphological difference in the diameter of the optic canals in patients with asymmetric papilledema.

The optic canal consists of 2 components: bone and meningothelial cells (2). Although bone is rigid, the meningothelial cells of the pia-arachnoid react to a variety of biological and mechanical stimuli (3,4). For example, increased intracranial pressure (ICP) causes proliferation of the number of meningothelial cells as well as an increase in their size (4). This, in turn, can result in thickening of the meningothelial cell layer, leading to narrowing of the subarachnoid space (SAS) surrounding the optic nerve and, eventually, to optic nerve compartmentation, perhaps protecting the optic nerve from the effects of increased ICP. This process has been demonstrated in an animal model (5) as well as in patients with papilledema who have undergone computed tomographic cisternography before and after intrathecal (spinal) injection of iodinated contrast material (6,7). In these patients, there is a decreased gradient of contrast between the lumbar SAS and the SAS surrounding the optic nerve (7). It would be interesting to see whether the Frisén grade of papilledema correlates with the contrast gradient. A further interesting aspect of the work by Bidot et al is that the visual field in the eye with the larger optic canal was more affected, although visual acuity was the same in both eyes. This finding also suggests that compartmentation might offer at least a temporary protective effect on the optic nerve; however, the effect of chronic compartmentation on cerebrospinal fluid circulation needs to be studied further.

In addition to patients with increased ICP and papilledema, it might be worthwhile assessing the diameters of the optic canals in astronauts in whom optic disc swelling has developed during prolonged spaceflight (8) and comparing them with the optic canals of astronauts who never developed optic disc swelling. If the size of the optic canal is a major determinant of whether or not an individual develops optic disc swelling from increased ICP or another cause, one would expect that astronauts in whom disc swelling has been observed should have larger canals than those in whom optic disc swelling has not developed.

In the meantime, we agree with Bidot et al that asymmetry of the diameter of the bony optic canal may produce a compartmentation phenomenon that protects the optic nerve from the effects of increased ICP and would add that it is possible that an increase in the thickness of meningothelial cell layer caused by a reaction to increased ICP may play a role as well, both in this setting and possibly in other optic nerve disorders (9).

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Asymmetric Papilledema in Idiopathic Intracranial Hypertension: Response

We thank Killer et al for their comments on our article (1) and for sharing their expertise on the emerging concept of compartmentation of the perioptioc subarachnoid spaces (2). We believe that compartmentation of the perioptic subarachnoid spaces probably plays an important role in the development of papilledema by interfering with the transmission of the cerebrospinal fluid (CSF) pressure between the intracranial subarachnoid spaces and the lamina cribrosa. Our results may provide a new insight into the underlying mechanisms and the potential consequences of the compartmentation in idiopathic intracranial hypertension (IIH), by protecting the optic disc from increased CSF pressure. This is likely not specific to IIH, and we agree with Killer et al that the optic canals might also play a role in other ocular conditions in which a disorder of the CSF pressure has been suggested, such as optic disc edema after prolonged spaceflight (3), or in glaucoma.

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Improvement on Automated Perimetry After Surgery for Idiopathic Intracranial Hypertension: Comment

We read with interest the article by Rizzo et al (1) entitled “Perimetry, Retinal Nerve Fiber Layer Thickness and Papilledema Grade After Cerebrospinal Fluid Shunting in Patients With Idiopathic Intracranial Hypertension” (1). We appreciate their efforts to establish better evidence for the efficacy of surgical intervention in the treatment of idiopathic intracranial hypertension (IIH) patients who are refractory to medical management. We were surprised to see them state in the article that “there are no case series of automated perimetry outcomes after cerebrospinal fluid (CSF) shunting in IIH patients.” We believe this statement is incorrect; we reported visual outcomes including perimetric mean deviation in a retrospective series of IIH patients who underwent either optic nerve sheath fenestration (ONSF) or CSF diversion (shunt) at our institution (2). Preoperative and postoperative visual acuity and perimetric mean deviation (MD) were shown, and we demonstrated that patients in both groups improved. It is quite interesting that the mean improvement of 5.63 dB in the study by Rizzo et al is very similar to the 6.57 dB improvement we found in our series of shunted patients. In fact, although the final perimetric MD in the ONSF cohort was worse than that in the shunted group, a mean improvement of 6.21 dB was seen for ONSF as well. This finding suggests that there may be a limit to the improvement in visual function that can occur after any surgical intervention for papilledema and vision loss; alternatively, it may mask a bimodal distribution of patients with minimal improvement and those in whom marked recovery occurs.

Patient selection bias remains a limiting factor in the interpretation of data in all of our retrospective analyses. We look forward to planned prospective studies that may help us to better serve our patients with this sight-threatening disease.

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REFERENCES

Improvement on Automated Perimetry After Surgery for Idiopathic Intracranial Hypertension: Response

We thank our colleagues for drawing attention to their experience with cerebrospinal fluid shunting in idiopathic intracranial hypertension patients. When our article was initially submitted to the Journal of Neuro-Ophthalmology, the article by Fonseca et al entitled “Visual outcomes of surgical intervention for pseudotubercular cerebri: optic nerve sheath fenestration versus cerebrospinal fluid diversion” had not yet been published. We appreciate the authors taking the time to compare and contrast their results with ours. We also look forward to the results of prospective studies on this topic.

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Improvement on Automated Perimetry After Surgery for Idiopathic Intracranial Hypertension: Comment

We read with interest the article by Rizzo et al (1) entitled “Perimetry, Retinal Nerve Fiber Layer Thickness and Papilledema Grade After Cerebrospinal Fluid Shunting in Patients With Idiopathic Intracranial Hypertension” (1). We appreciate their efforts to establish better evidence for the efficacy of surgical intervention in the treatment of idiopathic intracranial hypertension (IIH) patients who are refractory to medical management. We were surprised to see them state in the article that “there are no case series of automated perimetry outcomes after cerebrospinal fluid (CSF) shunting in IIH patients.” We believe this statement is incorrect; we reported visual outcomes including perimetric mean deviation in a retrospective series of IIH patients who underwent either optic nerve sheath fenestration (ONSF) or CSF diversion (shunt) at our institution (2). Preoperative and postoperative visual acuity and perimetric mean deviation (MD) were shown, and we demonstrated that patients in both groups improved. It is quite interesting that the mean improvement of 5.63 dB in the study by Rizzo et al is very similar to the 6.57 dB improvement we found in our series of shunted patients. In fact, although the final perimetric MD in the ONSF cohort was worse than that in the shunted group, a mean improvement of 6.21 dB was seen for ONSF as well. This finding suggests that there may be a limit to the improvement in visual function that can occur after any surgical intervention for papilledema and vision loss; alternatively, it may mask a bimodal distribution of patients with minimal improvement and those in whom marked recovery occurs.

Patient selection bias remains a limiting factor in the interpretation of data in all of our retrospective analyses. We look forward to planned prospective studies that may help us to better serve our patients with this sight-threatening disease.

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The authors report no conflicts of interest.

REFERENCES

Improvement on Automated Perimetry After Surgery for Idiopathic Intracranial Hypertension: Response

We thank our colleagues for drawing attention to their experience with cerebrospinal fluid shunting in idiopathic intracranial hypertension patients. When our article was initially submitted to the Journal of Neuro-Ophthalmology, the article by Fonseca et al entitled “Visual outcomes of surgical intervention for pseudotumour cerebri: optic nerve sheath fenestration versus cerebrospinal fluid diversion” had not yet been published. We appreciate the authors taking the time to compare and contrast their results with ours. We also look forward to the results of prospective studies on this topic.

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The author reports no conflicts of interest.
Fanfare for the Uncommon Neuro-Ophthalmologist: 
A Tribute to Irma Miller Lessell

The last 2 decades of the 20th century represented the golden years for neuro-ophthalmology. The field found its identity and was recognized as a specialty requiring unique training, character, and intelligence. Neuro-ophthalmology developed its voice with the founding of North American Neuro-Ophthalmology Society, International Neuro-Ophthalmology Society, and numerous other guilds, representing specific interests and regions within the field. During that time, an explosion of young talent burst on the scene, most of them trained by a handful of well-known mentors, now considered the founders of neuro-ophthalmology. Among them was Simmons Lessell MD at Harvard Medical School, whose protégés have risen to leadership positions in the new century. What these former fellows of Dr. Lessell say is that their fellowship was really under the tutelage of 2 Drs. Lessell—Simmons and Irma. They were dependent on one another, and the fellows were dependent on both. Sadly, Dr. Irma Miller Lessell died in August 2014 at age 79, only 8 months after pancreatic cancer was discovered.

At meetings, Irma tended to sit knitting near the podium like Madam Lafarge at the guillotine. A colleague once remarked that Irma was most likely accomplishing more than anyone else in the auditorium, and he was probably correct. Irma lived several lives: as a wife, a mother, a doctor, and a scholar. As a student, she excelled at every level and became only the third person to receive the MD degree summa cum laude at her medical school despite the fact that she did not begin medical school until she was 38. During the 17-year hiatus between the end of college and the start of medical school, Irma became the homemaker.

Irma was a balabusta (literally owner of the kitchen), a Yiddish noun that conveys her passion and focus better than the English equivalent. A balabusta’s house is spotless and orderly, the pantry well-stocked, her cooking exceptional, and a gracious hostess. A woman who could do nothing in moderation, Irma’s kitchen, large as it was, could not begin to accommodate all of the nonperishables she accumulated: spices lined the stairs down to the basement where enough canned food was available to easily survive a long siege. She never ran out of anything. Irma, for whom boiling an egg was a challenge when she first married, became an exceptional cook and even catered her 4 sons’ bar mitzvahs; 3 of them while she was a medical student! She took great pride in her formal dinners, for which she would write out the menu in calligraphy. She was a cookbook collector with hundreds of volumes filling the bookcases in almost every room in the house and overflowing onto the floor in most of them.

Besides cooking, Irma indulged in other hobbies such as needlepoint, shopping, and, of course, fishing. Anyone who was lucky enough to fish with her can testify to her skill and enthusiasm. While on the water, she kept a heavy camera with a long lens around her neck so that she would not miss an opportunity to capture a beautiful plant or bird. In keeping with her principle of doing nothing in moderation, she bought every item of fishing equipment and paraphernalia known to man (or woman). There were perhaps 10 items attached to her lanyard. The pockets on her fishing vest were brimming with fly boxes and other items that she viewed as requisites including a complete make-up kit, brushes, combs, and nail files. Irma took great pride in her appearance and adorned herself with bracelets, rings, necklaces, and pins at all times even when fishing, sleeping, or bathing. A woman living in a man’s world, she refused to give up her femininity and stated at a young age that if she ever had the money, she planned to be a clothes horse. It is fair to say that she achieved that goal: she accumulated clothes the way a philatelist collects stamps. Even though she might never actually wear an item, she took pleasure in owning it.

With the encouragement of her friends and family, Irma decided to go to medical school at the age of 38. She spent
years listening to physicians tell medical stories at parties and finally decided that it was her turn to take part. Having been greatly influenced by Norman Geschwind, she chose Neurology expecting to concentrate on higher functions, which at the time meant aphasia and related phenomena and not dementia as it does now. During residency, however, she surprised herself and the faculty by changing course and deciding to do pediatric neurology. In her practice, she alloyed neuro-ophthalmology with pediatric neurology. Irma was a gifted diagnostician, and she took special delight in diagnosing glaucoma, a maculopathy or a detachment that had been missed by the referring ophthalmologist who thought mistakenly that the patient had neurogenic visual loss. She remained a scholar, and, throughout her career, she played a significant role in the education of the trainees, some of whom grew to see her as a surrogate mother, albeit one with whom they could discuss cases and neuro-ophthalmology while keeping up with them drink for drink (If she was sufficiently inebriated, Irma would develop downbeat nystagmus which she enjoyed displaying as a neuro-ophthalmic party trick). The fellows loved her most of all because she would sneak in reprints of papers on topics on which she knew they would be quizzed. The fellows reveled in surprising Simmons by citing obscure but pertinent references thanks to her assistance.

Irma did not seem outwardly to be an ardent feminist but while she did not “talk the talk,” she certainly “walked the walk.” In her first job after college as an electron microscopy technician in the laboratory of the distinguished and world renowned chair of anatomy, she quit on the spot when he told her to bring him coffee. When the Lahey Clinic was wooing her, the president, who was a true martinet, interviewed her. He bragged to her that the clinic had many female physicians. Irma had the temerity to correct him, pointing out that he was wrong: she had reviewed the staff list and there were only 3. One time, she approached her chairman and asked whether it was just a coincidence that she, the lowest paid member of the department, happened to be the only woman. She got her raise. She refused to be treated as less-than because she knew she was not. By simply acknowledging her own skill and worth, Irma helped to change the way women are treated in medicine.

After a fruitful career, Irma retired from medicine and returned to her alma mater, Wellesley, where she devoured courses in the subjects that would redress the deficiencies of the premed curriculum. As always, she bought and read every available book or article; took, read, and re-read meticulous notes. She even planned her vacations so that she did not miss a single class. In the event that she had to miss a day, she had another student to record the lecture for her so she would never be behind. She accumulated so many credits in retirement that she could nearly have qualified for a second bachelor’s degree had she formally enrolled.

There are many very bright people, but among them, scholars are the exceptions. Irma was truly a scholar, hungry for knowledge, and prepared to expend energy to delve deeply. She was nearly, but not quite, a polymath because she eschewed subjects that did not interest her, as any intelligent person should do.

Irma and Simmons, her husband of 59 years, loved an Etruscan sarcophagus in the Boston Museum of Fine Arts because the relief on the lid depicts a husband and wife lying in bed covered only by a diaphanous cloak, still gazing at each other and touching after the passage of millennia. They saw themselves like the Etruscan couple and wished that it would never end. For the rest of us, losing Irma Lessell means losing a mentor, a scholar, and a friend. She changed the lives of everyone she knew with her fierce passion and surprising gentleness. There are no words to describe the great loss her friends and family feel at her death, all that is, left is this a piece of advice borrowed from the parable of the good Samaritan in the gospel of Luke: “Go and do thou likewise.”

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Martin Lubow, MD (1931 – 2015)

Marty was born in New York in the same hospital where his wife was born 6 months later! They didn’t meet until they were young adults. He studied at the Bronx Science High School, then transferred to California to be with his brother (who was in the service), finishing high school at Hamilton High School, Los Angeles. After graduating from UCLA, he went to medical school at the University of California at San Francisco (located at Berkeley at that time). He became an ophthalmology resident at the University of Pennsylvania in Philadelphia.

Marty always felt honored to be in the first class of neuro-ophthalmology fellows in San Francisco, taught by Dr. William F. Hoyt. There were only three neuro-ophthalmologists in the USA: Boston’s David Cogan, Baltimore’s Frank Walsh, and San Francisco’s William Hoyt. Marty served as a neuro-ophthalmologist at Letterman Medical Center (Army). As an Army physician, he served as recently as 2001 in Fort Belvoir following 9/11.

The first Hoyt neuro-ophthalmology fellows were “dispersed” throughout the USA to teach this new sub-specialty. Marty was recruited to the Ohio State University (OSU) by Dr. George Paulson, the OSU Neurology Professor and Chair who trained at Duke and recognized the value of having a neuro-ophthalmologist at a “quality” medical school (Fig. 1).

Marty and his wife Diane had a son, Alan, and daughter, Lauren. Diane was a great supporter of the arts and the Columbus Art Museum, where she was a docent. She predeceased Marty. Both Alan and Lauren started their college careers at Miami of Ohio, then on went to graduate school. Alan is now a physician in Denver and Lauren an attorney at Ohio State.

In his young career in the 1970s, Marty wrote about eye movements, coined the term WEBINO (wall-eyed bilateral internuclear ophthalmoplegia), popularized the use of acetazolamide and weight loss for pseudotumor cerebri in an article co-authored with Lora Kuhr, MD, and described pseudopapilledema in juvenile diabetics as “diabetic papillopathy” in a paper with OSU ocular pathologist Torrence (Todd) Makley, MD. For over 30 years, Dr. Lubow took care of patients at OSU and teaching medical students and residents.

After retiring from clinical practice, Marty “re-booted”: he loved doing research with ophthalmologists, rheumatologists, pathologists, vascular biologists, and bio-medical engineers. He published 13 articles from 2007 through 2015. Neuro-vascular research was his major passion. He studied Susac syndrome of microangiopathy and endotheliopathy with John Susac, MD and Robert Rennebohm, MD (Rheumatology, Cleveland Clinic), Cynthia Magro, MD (Dermatopathology, New York Weill Cornell), W. James Waldman, Ph.D. and Debbie Knight, M.S. (OSU Pathology). He studied retinal angiography patterns in various optic neuropathies and retinal conditions with OSU’s neuro-ophthalmologists Sue Benes and Steven Katz, retinologists Colleen Cebulla, Fred Davidorf, Mitch Opremcak, Matthew Ohr, and Alan Letson. In the last two years, he studied other vasculitides, capillary leak syndromes involving the eye and brain, giant cell arteritis and granulomatosis with polyangiitis (Wegener) with Brian Younge at Mayo Clinic, Cornelia Weyand at Stanford and her vasculitis research team including pathologist Gene Berry, and OSU glaucoma specialist Paul Weber.

Marty explored anatomy/surgical procedure development projects in the cadaver lab, proposing an orbital roof fenestration for high cerebrospinal fluid pressures affecting vision. His arachnoid villus anatomic research included brain studies with the OSU pathologists, and arachnoid cell cultures pump and drainage function studies with bio-engineer Deb Gryzbowski and her bio-engineering team at OSU (Fig 2).

Marty was a real character, an eccentric bicyclist, a gardener, an alternative energy advocate, a tough critic in written and verbal communication, an often dogmatic teacher. In 1975, he told his colleague Fred Davidorf that the invention of the CAT scan “was going to be the end of
neuro-ophthalmology” as the images would replace the elegance of history-taking and a classical detailed neuro-ophthalmology exam. He would quip after a resident’s presentation that “no one is completely worthless; they can always serve as a bad example”, while still helping that resident get established in a strong career after all. Many of us have classic “Marty stories”.

Marty Lubow passed away, surrounded by his family and colleagues, on February 12, 2015. He is survived by his two children and 3 grandsons. He will be greatly missed.

Selected Articles published by Dr Lubow:


Cited as coining the term WEBINO (wall-eyed bilateral internuclear ophthalmoplegia) in Hoyt and Daroff’s “The Control of Eye Movements”, 1971.


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FIG. 2. Martin Lubow and the arachnoid villus research team.
The Intersection of Optics and Neuro-Ophthalmology: The Enigma of Pseudophakic Dysphotopsia: Erratum

In the article that appeared on page 109 of the June 2015 issue of *Journal of Neuro-Ophthalmology*, a reference is listed incorrectly. The corrected reference is:

Kinard et al (8) reported in a study of pseudophakic patients without confounding ophthalmic disease and with excellent visual acuity, that a visual function questionnaire correlated strongly with patient dissatisfaction from pseudophakic dysphotopsia.


REFERENCE


The 41st Annual Meeting of the North American Neuro-Ophthalmology Society: Erratum

In the article that appeared on page e13 of the June 2015 issue of *Journal of Neuro-Ophthalmology*, a typographical error appeared within the fourth paragraph. The corrected paragraph is:

This year’s optional symposia also were popular. A number of our colleagues gave us a “tour” of International Neuro-Ophthalmology during a session chaired by Christian Lueck and Klara Landau. Mitch Strominger led a hands-on workshop on “Prism Therapeutics in Diplopia.” Betty Kovacs from the St. Luke’s Weight Loss Center in New York City and Shana McCormick from the University of Pennsylvania gave attendees practical ways to assist our obese patients (adult and pediatric) regarding weight loss. Janet Rucker and David Newman-Toker led the sold-out “Eye Movement and Vestibular Skills” session. In addition, we learned about many new neuro-ophthalmic research directions in both the scientific platform and poster sessions.

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